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THE STEROID HORMONAL MILIEU OF THE HUMAN FETUS AND MOTHER AT 16-20 WEEKS OF GESTATION.

The inter-relations of steroid hormone levels in plasma from mothers and their undisturbed fetuses during the second trimester of human pregnancy have not been defined previously. Maternal vein (MV), fetal artery (FA), fetal vein (FV) and amniotic fluid (AF) levels of progesterone (P), 17-OHP, 11 deoxycortisol (S), DOC, cortisone (E), cortisol (F), corticosterone (B) and aldosterone (Aldo) were measured in microassays in 12 conscious but sedated mothers and their fetuses undergoing therapeutic termination of pregnancy at 16-20 weeks gestation. The study received the approval of the Hospital Ethical Committee and maternal consent for the studies was obtained in each case. FA and FV samples were obtained by direct vessel puncture through a fetoscope without fetal disturbance. FA levels of F and B were significantly higher ($p<0.01$) than in FV; FV levels of P and E were higher ($p<0.01$) than FA values. No significant differences between FV or FA were found for levels of DOC, 17-OHP or S. MV levels of Aldo, F and B were significantly higher, with values of P, 17-OHP, DOC and S significantly lower than those in either fetal vessel. AF values of F, B, S, Aldo and DOC tended to be lower than those reported previously from mothers undergoing routine amniocentesis. We conclude: there is evidence that the fetal adrenal cortex is functioning independently of the mother in mid-gestation; maternal premedication may lower fetal stress hormone secretion.

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CONCOMITANT DETERMINATION OF AMNIOTIC FREE ALDOSTERONE (FAldo) AND ITS 18-OXO-GLUCURONIDE (GAldo) AND MATERNAL PLASMA ALDOSTERONE (PAldo) THROUGHOUT NORMAL PREGNANCY.

Concentrations of FAldo and GAldo were simultaneously measured by specific RIA in 84 samples of human amniotic fluid (AF) collected between 15-34 weeks in normal pregnancies. PAldo was concomitantly determined by RIA on samples obtained at 14.00 hr, after two hours decubitus. PAldo showed a significant rise during pregnancy, its level averaging 134.5 ± 10.8 pg/ml (mean ± SEM) before 20 weeks ($n = 62$) and 288.2 ± 49.2 pg/ml between 20-34 weeks ($n=22$) ($p < 0.01$). In AF, the increase of GAldo during the second stage of pregnancy largely exceeded that of FAldo rising from 81.2 ± 5.7 pg/ml to 269.5 ± 61.2 pg/ml and from 84.0 ± 5.9 pg/ml to 118.8 ± 11.5 pg/ml for the latter between the 15-20 weeks and 20-34 weeks periods. A significant relationship between AF levels and age of pregnancy could only be detected for GAldo ($r= 0.691$, $p<0.01$). Our results agree with patterns of PAldo (Weir et al, 1974, Ledoux et al, 1975) and FAldo (Blankstein et al, 1980, Sippell et al, 1981) already reported. The increase of GAldo presently described disagrees with its high and stable level reported by Aderjan et al (1977) on poorly documented data. Simultaneous determination of F- and G-Aldo shows that the rate of increase of fetal aldosterone production is higher than could be expected from estimation of FAldo alone. Augmentation of GAldo in AF probably expresses both the increased contribution of urine to AF and the maturation of renal glycuronoconjugation process.

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Water Metabolism in Preterm Infants during the first Week of Life and its Regulation by Arginine-Vasopressin (AVP).

We studied the role of AVP in the water metabolism of preterm infants with a sensitive urinary AVP RIA. Three groups were studied. GroupA: 16 orally fed infants from 32 to 38 weeks of gestation. GroupB: 6 infants with parenteral fluid administration from 32 to 36 weeks of gestation. GroupC: 12 infants, ventilated for RDS from 28 to 36 weeks of gestation with parenteral fluid administration. Gr.A received 50±9 ml/kg on day 1 with daily increasing amounts up to 169±17 ml/kg on day 7 p.o. They had small urine volumes with high osmolality and lost up to 9% weight. AVP was stimulated by this water loss from 15.3±4.3pg/ml on day 1 to 36.6±27.2pg/ml on day 3-5. GrB received initially greater fluid volumes i.v. (109±10 ml/kg on day 1). They produced more urine with low osmolality and did not loose weight. AVP was suppressed from 13.1±11.4pg/ml on day 1 to 5.4±3.5pg/ml on day 2. GrC received on day 1 already 121 ±21ml/kg. The infants gained weight up to 107.5±6.3% on day 3 while serum Na decreased to 133 mmol/l. Urine volume was inadequate low as was urine osmolality inadequate high. AVP was 21.0±18.7pg/ml on day 1 and was not suppressable until day 3. There was a significant ($p=0.05$) correlation between 1min Apgar scores and AVP as well as FiO_2 and AVP on day 1. No significant correlation was found between mean respiratory pressure and AVP. We conclude, that infants with RDS have a nonosmotic release of AVP and should receive smaller fluid volumes in the first three days of life.

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GROWTH HORMONE (GH) RESPONSE TO THYROTROPIN-RELEASING HORMONE (TRH) DURING PUBERTY: A REAPPRAISAL.

A paradoxical GH response to TRH has been described in constitutional tall stature. Bromocriptine (BR) therapy has consequently been proposed to reduce adult height prediction in tall but otherwise normal children. This study evaluates the GH response (0-180min) to a single dose (0.2mg) of TRH ($n=59$) in 11 tall children followed prospectively before (A1) and after (A2) 6 months of treatment with BR (5mg/d), while still on therapy, in 9 children of average height (B), 12 with precocious puberty (C), 9 with delayed puberty (D) and 7 with GH deficiency (E). Peaks of GH (> 5ng/ml) were observed in 92.3% of cases from groups A to D, whereas none occurred in group E. They occurred mainly beyond 120 minutes (57.6%) and were of similar magnitude in groups A1, A2 and B. In addition, a bifid secretion pattern occurred in 43.5% of cases. In these patients, the early peak was unrelated to stress (normal prolactin). In conclusion, the mode of GH response as well as GH peak amplitude following TRH remain similar in tall and in average height children who are matched for bone age. In group A2, BR failed to modify the GH secretory pattern following TRH injection. The pattern of GH secretion observed after TRH might be the expression of its normal amplified pulsatile secretion mode during puberty and thus be independent of TRH.

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THE MECHANISM OF THE ADOLESCENT GROWTH SPURT INDUCED BY PULSATILE GnRH TREATMENT

We have induced puberty in 26 patients (12M, 14F) using low dose pulsatile GnRH for 0.8 to 1.6 years. Progress was monitored by serial overnight profiles for gonadotrophins, GH and sex steroids at 15 minute intervals. GnRH 2 or 4ugs was administered subcutaneously at night at 90 minute intervals. In order to maintain normal pubertal development, GnRH pulse amplitude was progressively increased and/or treatment was administered throughout 24 hrs. We have succeeded in mimicking all the endocrine and clinical events of puberty including the timings of the adolescent growth spurts.

Girls showed early growth acceleration with an increase in GH secretion from the first week of treatment. After breast stage 4 had been attained, GH pulse amplitude varied with the state of ovarian follicular development. By contrast, boys showed a decelerating growth velocity and diminishing GH pulse amplitude at the start of treatment, even though sex steroid secretion increased progressively. When a 10ml testicular volume had been attained there was a marked increase in GH pulse amplitude coincident with the pubertal growth spurt. In both sexes GH secretion was modulated by changes in pulse amplitude without alteration in pulse frequency.

These observations explain the differences in timings of the onset of the adolescent growth spurts of girls and boys.

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GROWTH HORMONE SECRETION ON COMPLETION OF TREATMENT IN ISOLATED "IDIOPATHIC" AND POST-IRRADIATION GROWTH HORMONE DEFICIENCY.

After completion of growth hormone (GH) treatment, 19 patients with isolated "idiopathic" growth hormone deficiency (IGHD) and 15 with post-irradiation growth hormone deficiency (PRGHD) were asked to undergo retesting of GH secretion with an insulin tolerance test and/or an arginine stimulation test. PRGHD patients are those with CNS tumours distant from the hypothalamic-pituitary axis (n=13) or acute lymphatic leukaemia (n=2), who had received cranial or cranospinal irradiation.

All 15 patients with PRGHD remained GH deficient [peak GH level <7mU/l (n=10) and 7-15mU/l (n=5)]. However of the 19 retested IGHD patients, 5 (26%) had peak GH responses >15mU/l (regarded now as transient or false F-IGD) and were indistinguishable from the remainder [permanent or true T-IGHD, peak GH levels <7mU/l (n=12) and 7-15 mU/l (n=2)] by pre-treatment anthropometry and post-treatment height SDS, but had a lower first year height velocity (Mean Velocity 5.4cm/yr ±0.9 for F-IGHD v 8.7cm/year ±1.75 for T-IGHD $p<0.01$) and height acceleration on treatment (Mean acceleration 2.1cm/yr ±1.7 for F-IGHD v 5.2cm/yr ±2.3 for T-IGHD $p<0.05$). By current practices 2 F-IGHD patients may have been distinguished by sex-steroid priming.

Thus post-irradiation GH deficiency appears to be permanent but errors of diagnosis in IGHD are common.