

- 487** THE EFFECT OF LOW DOSE ESTRADIOL ON 6 MONTH GROWTH RATES IN PATIENTS WITH TURNER'S SYNDROME JL Ross, L Long, M Skerda, F Cassorla, D Kurtz, GB Cutler, Jr. Dept. Pediatrics, Hahnemann Univ., Phila, NICHD, NIH, MD (spon by R. Kaye)
- We previously noted a biphasic dose-response curve for ethinyl estradiol (EE<sub>2</sub>) on short term growth in girls with Turner's syndrome. Optimal growth occurred at the dose of 100 ng/kg/d (4 ug/d in a 40 kg girl). In the current study we asked whether the growth stimulation at the dose of 100 ng/kg/d would be sustained during a 6 month period and whether bone age advancement would be accelerated. We randomly assigned 16 girls with Turner's syndrome, age 5 to 15 y, to treatment with 100 ng/kg/d EE<sub>2</sub> or placebo for 6 months, after observing basal growth for 2 months. We assessed growth by the 4-week lower leg growth rate (LLGR), and by height measurements, and we determined bone age at the beginning and end of treatment. The results are shown below.
- | (mean ± SE)     | LLGR         |             | Height       |            | ΔBone age/<br>Δtime |
|-----------------|--------------|-------------|--------------|------------|---------------------|
|                 | (mm/4 weeks) | Rx          | (cm/4 weeks) | Rx         |                     |
| Placebo         | .98 ± .33    | 1.14 ± .53  | .35 ± .05    | .26 ± .05  | 1.27 ± .13          |
| EE <sub>2</sub> | 1.07 ± .40   | 1.50 ± .46* | .24 ± .05    | .41 ± .20* | 1.21 ± .13          |
- \*p<0.05, placebo vs. EE<sub>2</sub> (one-tailed t-test).
- Low dose EE<sub>2</sub> stimulated growth over a six month period without advancing bone age relative to placebo. Breast development advanced one Tanner stage in 2 of the 8 EE<sub>2</sub> treated patients. Serum somatomedin C concentrations did not change significantly during treatment. We conclude that ethinyl estradiol at the dose of 100 ng/kg/d for 6 months produces sustained growth without bone age acceleration in girls with Turner's syndrome.

- 488** IN VITRO SYNTHESIS OF 1,25 DIHYDROXYVITAMIN D<sub>3</sub> (1,25) AND 24,25 DIHYDROXYVITAMIN D<sub>3</sub> (24,25) BY FETAL (F) AND MATERNAL (M) SHEEP KIDNEYS. Richardus Ross, (Spon. by Jean J. Steichen) Univ. of Cincinnati College of Medicine, Dept. of Pediatrics, Cincinnati, Ohio.
- Near term ovine pregnancy is characterized by F:M transplacental plasma gradients of 1,25 [70±7 (F) v 48±4 (M) pg/ml, n=19, p<0.001] and 24,25 [1261±189 (F) v 839±74 (M) pg/ml, n=10, p<0.05]. The relative contributions of placental transfer, placental synthesis and fetal synthesis to fetal plasma levels of these metabolites are presently unclear. To further elucidate the role of fetal synthesis, homogenates of fetal and maternal renal cortex were incubated in vitro with <sup>3</sup>H-25 hydroxyvitamin D<sub>3</sub> (25 OHD<sub>3</sub>) to assess 25 OHD<sub>3</sub>-hydroxylase enzyme activities. Products were identified by co-migration on HPLC with authentic 1,25 and 24,25.
- |               | 1,25 synthesis<br>(pM/g/min) | 24,25 synthesis<br>(pM/g/min) |
|---------------|------------------------------|-------------------------------|
| Fetal(n=5)    | 8.20±0.16                    | 1.79±0.20*                    |
| Maternal(n=5) | 11.08±0.85                   | 1.23±0.14                     |
- p<0.001 (1,25 versus 24,25)
- All data is expressed as mean ± SEM. The predominant metabolite formed by both fetal and maternal tissue was 1,25. There were no differences between fetal and maternal synthesis rates for either 1,25 or 24,25. However, these synthesis rates, when extrapolated to account for differences in 1) maternal and fetal renal mass and 2) maternal and fetal plasma volume, could wholly account for the fetal plasma levels and transplacental gradients of these metabolites observed in vivo.

- 489** DECREASE IN GROWTH HORMONE (GH) AND SOMATOMEDIN C (SOMC) DURING LHRH AGONIST (LHRHa) TREATMENT OF CENTRAL PRECOXIOUS PUBERTY (CPP), Craig R. Rudlin, M. Joan Mansfield, John F. Crigler, Jr, Karin A. Karol, John D. Crawford, Paul A. Boepple, William F. Crowley, Jr, Harvard Medical School, Div. of Endocrinology, Children's Hospital, Reproductive Endocrine Unit, Mass. General Hospital, Boston
- LHRHa suppresses both gonadotropin pulsations and sex steroids and slows height velocity (HV) in patients with CPP. To evaluate GH's role in this slowing of growth, sleep induced GH secretion (20 min samples, 10 PM - 2 AM) and SOMC (10 PM) were measured in 9 pre-adrenarchal girls with CPP (ages at onset 1.6-6.3 yrs, M=3.8; bone ages advanced a mean of 3.7 yrs). Therapy suppressed gonadotropin pulsations, response to LHRH, estradiol and maturation indices in all patients. Growth velocity fell from 14.4 ± 1.7 cm/yr (Mean ± SEM, all measurements) pretherapy to 8.7 ± 1.4 after 6 mos of therapy (p=0.0005). SOMC levels decreased from 3.1 ± 0.7 IU/ml pretherapy to 1.3 ± 0.2 at 3 mos (p=0.009) and 1.4 ± 0.2 at 6 mos (p=0.007). Nocturnal peak GH levels fell from 25.4 ± 6.8 ng/ml pretreatment to 9.1 ± 1.7 at 3 mos (p < 0.01) and 7.5 ± 1.1 at 6 mos of therapy (p < 0.01). Total GH secreted during the 4 hr interval decreased a mean of 58% at 3 mos and 48% at 6 mos compared to pretreatment. The accelerated HV in CPP patients under 6 yrs is associated with increased GH and SOMC production. With LHRHa induced suppression of gonadal steroids, both HV and GH and SOMC production are decreased.

- 490** NEONATAL SCREENING FOR CONGENITAL HYPOTHYROIDISM: BENEFICIAL EFFECT OF EARLY DIAGNOSIS AND TREATMENT. Joseph Sack, Abraham Elicer, Rivka Sofrin, Rachel Theodor, Bernard Cohen. (Spon. by Gerald W. Fischer). Sheba Medical Center, Tel Hashomer Israel.
- It has been proposed that early diagnosis and treatment of congenital hypothyroidism (HYPO) based on neonatal screening will improve outcome. To test this hypothesis, we performed standard psychological tests (Gesell, Stanford Binet, Wechsler) in 3 groups of children with treated HYPO: 14 discovered by neonatal screening (SCRN) and 24 diagnosed prior to institution of screening (15 with thyroid agenesis (AGEN), 9 with ectopic thyroid (ECT)). Age at initial treatment (weeks) differed in the 3 groups (SCRN: 4.6 ± 0.8 (SEM); AGEN: 19.3 ± 4.0; ECT: 46.4 ± 8.3), although age at testing averaged 3.3 yrs in all 3 groups. The global DQ/IQ score was lowest in AGEN (82 ± 6; range 52-142), intermediate in ECT (93 ± 10; range 56-141) and highest in SCRN (104 ± 4; range 75-127). In the AGEN group, there was an inverse relationship between the age treatment was started and the subsequent DQ/IQ score (p < 0.05). This inverse relationship was not observed in the SCRN group, thus suggesting the effect of intrauterine hypothyroidism. We conclude that neonatal screening for congenital hypothyroidism results in earlier diagnosis than use of clinical criteria alone, and the consequent early treatment results in improved mental development. These data indicate the importance of prenatal detection and treatment of the hypothyroid fetus.

- 491** LOW DOSE ETHINYL ESTRADIOL (EE2) TREATMENT OF TURNER'S SYNDROME. Abdollah Sadeghi-Nejad, Anna Binkiewicz and Boris Senior. Tufts University School of Medicine, New England Medical Center, Boston.
- Short term studies in children with Turner's syndrome showed that EE2 in a dose of 100 ng/kg/day enhanced the rate of ulnar growth whereas a smaller dose was less effective and larger doses were inhibitory (Ross, et al, New Engl J Med 309:1104, 1983). We therefore treated 11 such patients (bone ages 8-15 years) with EE2 100 ng/kg/day for 3-12 months. Seven who had previously been treated with conventional doses of estrogen were taken off therapy for the preceding 3 months.
- All 4 previously untreated patients exhibited breast changes on therapy. Bone maturation did not accelerate and Somatomedin C levels did not increase. Only the 3 patients with the lowest bone ages showed an appreciable growth response with the youngest showing the greatest enhancement.
- | Bone age (year) | Growth rate, pre (cm/yr) | Growth rate, EE2 (cm/yr) |
|-----------------|--------------------------|--------------------------|
| mean 13.3       | 2.0                      | 1.8                      |
|                 | Eight Older Patients     |                          |
|                 | Three Younger Patients   |                          |
| #1 10.75        | 3.1                      | 5.2                      |
| #2 10.75        | 3.6                      | 5.7                      |
| #3 8.25         | 3.9                      | 8.0                      |
- We conclude that this dose of EE2 appears to be a potent growth stimulus if administered at an earlier age than estrogens are commonly employed. Furthermore, this tiny dose of EE2 does exert the usual systemic effects of estrogens.

- 492** STEROID SPECIFICITY OF RAT RENAL MINERALOCORTICOID RECEPTORS AFTER IN SITU PERFUSION. H. Sasano, K.O. Martin, M.I. New, Dept Pediatrics, The New York Hosp-Cornell Medical Center, New York 10021

Recently, elimination of CBG has been reported to result in higher binding affinity of corticosterone (B) to mineralocorticoid receptor (MR). We have studied binding affinities of rat kidney MR by cytosol and tissue slice methods after complete perfusion in situ. To estimate the degree of serum contamination in the cytosol, rat serum CBG and albumin level in cytosol were assayed by RIA. Perfused kidney cytosol contained less than 0.1 µl per ml serum contamination. In cytosol and slice experiments without blockade of the glucocorticoid receptor (GR), both Type I and II <sup>3</sup>H-aldosterone binding sites were present, indicated by the curvilinear pattern of Scatchard analysis. With RU-28362 as GR blockade, Scatchard plots were rectilinear. In perfused cytosol, all the corticosteroids tested (aldosterone, deoxycorticosterone, B, cortisol, dexamethasone) bound to MR with the same affinity in the presence of RU-28362, while non-perfused cytosol showed steroid specificity similar to those previously reported. Addition of increasing amount of rat serum to perfused cytosol decreased the binding of B to MR, indicating that B was bound to CBG, thus decreasing the availability of B for MR-binding. Slices of well-perfused kidney showed steroid specificities similar to the non-perfused cytosol.