486 STABLE BONE MINERAL CONTENT ASSOCIATED WITH RISES IN CALCITONIN & 1,25(OH)$_2$ VIT. D IN NORMAL PREGNANCY, Jerry Schutzman, Jean Steichen, Vicki Neumann, Mona Ho, Reginald C. Tsang, U. of Cincinnati.

Calcium regulating hormones have not been studied in relation to bone mineral content (BMC) during pregnancy. We hypothesized that bone mineral content would be correlated with calcitonin (CT) concentrations, since CT is considered a hormone protective of maternal skeleton during times of Ca stress; BMC also would be maintained in pregnancy because of elevation of 1,25(OH)$_2$ vit. D levels, which promotes bone Ca stores by increasing intestinal Ca absorption. 11 normal pregnancies in middle class women between 25-35 yrs. old were studied prospectively. Blood samples were drawn for analysis of iCa (ion specific electrode), 1,25(OH)$_2$ vit. D (HPLC, protein binding assay N= 29 ± SD 6 pg/ml) & CT (radioimmunoassay, 1-32 CT); monthly BMC were measured by photon absorptiometry. BMC (1/3 radius) was .787 ± SE .033 gm/cm, .781 ± .033, .819 ± .024 & .795 ± .027 at 8-11, 13-16, 23-27 & 33-37 wks (no significant change). iCa was 3.9 ± 1.14 mg/dl, 4.7 ± 1.02, 4.6 ± 1.01, 4.7 ± 1.00 (no significant change). 1,25(OH)$_2$D was elevated 57 ± 1, ($p<.001$ vs. non-pregnant), 72 ± 1, 64 ± 1, 91 ± 1, ($p < .1$). CT was 12 ± 1 pg/ml, rose to 18 + 1, 29 + 1, 32 + 1, ($p< .001$). BMC was not correlated with iCa or 1,25(OH)$_2$D; BMC was correlated with CT, after 12 wks. ($r = .42$, $p < .04$). Thus, bone mineral content is maintained during normal pregnancy; 1,25(OH)$_2$D is elevated early in pregnancy but not correlated with BMC; calcitonin rises > 12 wks. of pregnancy & correlates with BMC. We speculate that rises of calcitonin during pregnancy protects the maternal skeleton, & elevations of 1,25(OH)$_2$ vitamin D restore Ca balance during a period of calcium stress.

● 487 RESPONSE OF GROWTH HORMONE DEFICIENT PATIENTS TO SYNTHETIC GROWTH HORMONE-RELEASING FACTOR. Elizabeth A. Schriock, Robert H. Lustig, Stephen M. Rosenthal, Selna L. Kaplan, Melvin M. Grumbach, Dept. of Pediatrics, University of California San Francisco, San Francisco, CA

We studied the growth hormone (GH) response to synthetic growth hormone-releasing factor (GRF (1-44)-NH2)+ in non-GH deficient (NGHD) subjects (4-33 yrs) and GH deficient (GHD) patients (5-24 yrs). The mean (±SE) peak GH response of 6 NGHD children after 5 μg/kg IV of GRF (27.1±5.8 ng/ml) was similar to that of NGHD young men previously reported (JCEM 57:677). Of 20 patients with severe GH deficiency 17 responded to 5 μg/kg IV of GRF, but the mean peak plasma GH concentration was less than that of the NGHD group (5.0±1.2 vs 27.2±3.5 ng/ml; $p<0.001$). Patients with isolated GH deficiency had responses similar to those with multiple pituitary hormone deficiencies. The GH responses of the GHD children correlated negatively with chronologic age ($r= -0.758$, $p<0.02$). Six partially GHD children had a higher GH response to GRF than severely GHD children (13.1±1.8 vs 6.9±1.7 ng/ml; $p<0.04$) but lower than NGHD children ($p<0.05$). GRF induced higher plasma GH levels in GHD than did arginine, insulin, or L-dopa.

The GRF test is useful for assessing GH reserve. Although a GH response to GRF in GHD patients suggests GRF deficiency, the lack of response does not exclude it. The GH response to synthetic GRF in many GHD children is consistent with a hypothalamic abnormality as the etiology of their GH deficiency and supports the potential therapeutic usefulness of GRF or an analog in these patients.

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† 488 MECHANISM OF DECREASED INSULIN ACTION IN TYPE A FAMILIAL INSULIN RESISTANCE. W. Frederick Schwenk, Robert A. Rizza, Lawrence J. Mandarino, Alvin B. Hayles, Morey W. Haymond, Mayo Medical School, Mayo Clinic and Foundation, Depts. of Pediatrics and Medicine, Rochester, MN.

Type A insulin resistance (associated with acanthosis nigricans and ovarian dysfunction in adolescent females) has been ascribed to decreased insulin receptors or to a postreceptor defect. Four affected females from one family (including a set of twins) with acanthosis nigricans and varying degrees of male habitus, acral hypertrophy, and muscle cramps had normal oral glucose tolerance, but increased fasting (64-170 μU/ml; control 13±1 μU/ml) and peak post-glucose (244-1010 μU/ml; control 90±1 μU/ml) plasma insulins (IRI). To test for a post-receptor defect, the twins underwent euglycemic glucose clamps with plasma IRI varied from 65 to 1600 μU/ml. The insulin dose response curves were shifted to the right with 1/2 max IRI responses (Km) of 135 and 210 μU/ml vs. 72±8 μU/ml in controls. Glucose infusion rates required to maintain euglycemia at 1600 μU/ml (Vmax) were decreased (5.7 and 8.3 vs. 12.0±0.3 mg/kg·min in controls). Decreased insulin action was not due to anti-insulin receptor antibodies or obesity (as assessed by ^3H_2O). In the one twin in which it was measured, insulin binding to monocytes (7.0% per 10^7 monocytes) and erythrocytes (3.0 % per 1.6 x 10^9 RBC's) was less than that observed in controls (10.4±0.8 and 4.8±.5, respectively). Conclusion: Because of a decreased maximal response (Vmax) and sensitivity (Km) to infused insulin, type A insulin resistance may be due to both receptor and post-receptor defects. When a patient with type A insulin resistance is identified, a familial incidence should be sought.

† 489 CONGENITAL HYPOALDOSTERONISM DUE TO DEFICIENCY OF CORTICOSTERONE METHYL OXIDASE I (CMO-I) ACTIVITY. D Shulman, A Vargas, J Prebis, J Melby, T Wilson, A Root Dept.Ped., Univ.So.Fl.Col.Med., All Child.Hosp., St.Petersburg, FL.

Congenital isolated hypoaldosteronism is associated with salt-losing and failure to thrive in infancy. The terminal stages of aldosterone (A) synthesis require two mixed function oxidases: CMO-I and CMO-II. Corticosterone (B) is converted to a labile intermediate by CMO-I which is then converted to A by CMO-II. Absence of CMO-II activity results in low circulating levels of A and accumulation of 18-hydroxycorticosterone (18-OHB) generated from the labile intermediate. The normal ratio of 18OHB/A in both urine and plasma is 2. Ratios in infants with CMO-II deficiency have been >15. We now report an infant with CMO-I deficiency

A 5 week female infant presented with failure to thrive and hyperkalemia (10 mEq/L), hyponatremia (110), hyperrenninemia (804 ng/ml/hr) and hypoaldosteronemia (2.7 ng/dl). B was elevated (1128, 1013 ng/dl). Desoxycorticosterone (DOC) and 18-hydroxy-DOC levels were mildly elevated (25 and 21 ng/dl respectively). 18-OHB values were in the normal range (25, 22 ng/dl). Plasma ratios of 18-OHB/A were 2.5, 3.1. Urinary ratios of the metabolites of these compounds ranged between 2.3 and 2.6. ACTH did not increase A levels significantly (6.7→8.9), but B increased three-fold (473→1559). 18-OHB levels increased only to the high normal range (22→47). The clinical and biochemical abnormalities readily corrected with mineralocorticoid and salt. Low A levels in the presence of normal 18-OHB/A ratios in the salt depleted state constitute evidence for decreased CMO-I activity.

† 490 WHAT CONSTITUTES GH DEFICIENCY? Bessie E. Spiliotis, Gilbert August, Wellington Hung and Barry B. Bercu. Pregnancy Research Branch, NICHD, NIH, Bethesda, MD 20205 and Children's Hosp. National Med. Ctr., GW University.

Classic GH deficiency is defined on the basis of provocative tests in the appropriate clinical setting. Some authors have proposed that a suitable nocturnal GH level is a useful physiologic index in normal children. Using standard provocative as well as physiologic (q20 min x 24h) testing, we have studied 18 GH deficient and 11 short (ht <1%tile) control children. The GH deficient group was divided into 3 based on the highest peak GH after provocative tests: severe (< 5.0 ng/ml), moderate (5.0-6.9 ng/ml) and partial (7.0-9.9 ng/ml) GH deficiency. The data are summarized:

GH-deficient group	Peak GH after provocative tests (ng/ml)	Mean 24h GH conc. (ng/ml)	Number of patients with GH pulses between 10-19.9	20-29.9	>30 ng/ml
Severe (n=10)	2.6 ± 0.3*	1.5 ± 0.3*	3	2	0
Moderate (n=2)	6.6†	2.0†	1[a]	0	0
Partial (n=6)	8.4 ± 0.5*	1.6 ± 0.2*	2	0	1
Control Group (n=12)	21.2 ± 3.9	5.0 ± 0.7	11	11	5

[a]One pt with GH pulse during daytime, all other pulses nocturnal.
*$P < 0.005$, † $P < 0.025$ Control vs. GH-deficient group.

Our data confirm that GH deficiency can be diagnosed with standard provocative tests, however, physiologic GH measurements such as nocturnal (and even daytime) sampling can sometimes be misleading. Twenty-four hour studies (and integrated GH conc.) are helpful in better understanding the neuroregulatory control of GH secretion as well as giving a more precise analysis of GH output.

† 491 CHARACTERIZATION OF β-ENDORPHIN ACTIVITY IN THE FETUS: ACETYLATED β-ENDORPHIN (AC β-EP) AND TOTAL β-ENDORPHIN (β-EP) DURING HYPOXIA. Raymond I.Stark, Sharon L. Wardlaw, Salha S. Daniel, Mary M. Smeal and L. Stanley James, Columbia U., Coll.P&S, Babies Hosp., Div.Perin., Depts.Ped.& Anes., N.Y.

Hypoxia is associated with high concentrations of total plasma β-EP in both human umbilical cord and fetal lamb. To characterize this endorphin activity we used RIA to measure AC β-EP (antibody reacts <1% with β-EP) and total plasma β-EP (antibody reacts equally with β-EP and AC β-EP). 9 fetal lambs were studied before and after exposure of the pregnant ewe to 10% O_2 x 30 min with and without fetal dexamethazone pretreatment. In 13 hypoxia studies (PaO_2 22±1 to 12±1 mmHg), AC β-EP remained unchanged (85±11 and 109±14 pg/ml mean ±S.E.) while total β-EP increased (102±21 to 557±165 pg/ml, $p<.01$). Thus it is likely that inactive AC β-EP is the major endorphin species in the unstressed fetus while biologically active β-EP increases with hypoxia. In 5 hypoxia studies dexamethazone pretreatment had no effect on AC β-EP level while the increase in total β-EP was blunted (108±25 to 158±12 pg/ml). There was an inverse correlation of AC β-EP with gestational age ($R=-0.49$, $p<.01$, 113-142d, $N=28$). The total β-EP response to hypoxia was less before than after 130 d gestation. Thus biologically inactive AC β-EP released by the unstressed fetus in decreasing amounts toward term is unaffected by hypoxia or glucocorticoids while active β-EP release is increased by hypoxia and suppressed by glucocorticoids. Speculation: Data are consistent with diminution in tonic activity of intermediate (AC β-EP release) and enhancement of anterior β-EP release) pituitary activity with gestational maturation.