

Hypospadias and Early Gestation Growth Restriction in Infants

Reports from Europe and the United States have indicated that there is an increasing incidence of hypospadias. This study by Hussain et al involved two tertiary care neonatal intensive care units in Connecticut. It was a retrospective study of 14 years of admissions. It showed a 10-fold increase in hypospadias over the 14 years, from 0.4% of admissions in 1987 to 4% in the year 2000. The increased occurrence of hypospadias among premature infants was associated with intrauterine growth retardation. An increased frequency of hypospadias was also noted among the infants born in the lower percentiles (3rd to 25th).

An association of hypospadias with the smaller quartiles of head circumference (3rd to 25th) was also present. The frequency was highest in first-born infants and those born to older mothers. No association was noted with race, maternal diabetes, hypertension, or pre-eclampsia. No specific teratogens were identified. There

does not seem to be an increase of a particular recognizable syndrome in spite of the association with intrauterine growth restriction. The consistent involvement of all growth parameters, i.e., weight, length, and head circumference suggested that hypospadias is related to overall poor intrauterine growth.

Hussain N et al. *Pediatrics* 2002;109:473-478.

Editor's Comment: *A specific etiology for the observed increase in hypospadias does not seem to be forthcoming. These are obviously real concerns with such a striking change over the last decade. The question of endocrine disrupters and the association of advancing maternal age are important, but no real clarity exists as to their real role at this time.*

Judith G. Hall, OC, MD

Growth, Developmental Milestones, and Health Problems in the First Two Years in Very Preterm Infants Compared with Term Infants: A Population Based Study

Bucher et al report the results of a questionnaire sent to parents of Swiss infants born before 32 weeks of completed gestation. The parents were asked to answer questions concerning weight, body length, head circumference at 24 months of age, developmental milestones, eye and ear problems, long-term medications, fever, cough, and infectious diseases during the last 12 months. Information regarding developmental milestones is recorded in the Swiss Health Carnet given to each parent of a newborn infant. A comparison group for this study included two control infants for each index infant. The second was contacted if the first did not respond. Infants of multiple births or with severe malformations or syndromes were excluded. The control infants had to have been born in the same hospital, at term (after 37 weeks), and within 14 days of the expected date of birth of the index infant, and of the same gender as the index infant.

Three hundred nine infants born between January 1, 1996 and December 31, 1996 were included. Index infants had significantly lower body weight, body length, and smaller head circumference at 24 months *corrected* age as compared to their matched control. The mean weight difference at the age of 2 years (*corrected* for the very preterm infants) was 1.2 kg for boys, and 1.2 kg for girls. The mean difference in body length was 3.5 cm for girls and 3.3 cm for boys. Thirty-three percent of index infants were below the third percentile for length

at 24 months *corrected*. The difference in head circumference was small (0.7 cm), but statistically significant ($p < 0.001$). Height and weight parameters were similar in the parents of pre-term and term infants, and in agreement with normal growth standards for adults. In the very preterm infants, there was significant motor delay, increase in eye problems and in use of long-term medications, but no difference in infectious diseases during the prior 12 months. Sitting was not delayed, but walking (mean of 14.5 months vs 13.5 months in controls ($p=0.4$) and drinking out of a cup (50% of each group at 16.5 vs 13.5 months; $p<0.001$) were delayed. Of the very preterm infants, 16% were unable to walk independent at 18 months *corrected* age. These infants are at increased risk for developing cerebral palsy. The authors state that such a retrospective study can include much bias, but that has been accounted for by utilizing a significantly large control group. The cause of significant growth delay remains unclear. Suggested causes include: (1) decreased length of gestation; (2) insufficient supply of nutrients over prolonged periods of time after birth; or (3) intercurrent illnesses in the first year, such as chronic lung disease which may increase energy requirements and interfere with nutrient intake.

Bucher HU, et al. *Eur J Pediatr* 2002;161:151-156.

Editor's Comment: The authors recall several studies in which catch-up growth in pre-term infants has been stated to occur up until adolescence, and note that the patients in this study should be followed at least through school age. The data are intriguing however, for several other reasons. First, it is possible that these very young children (less than 30 weeks gestation) may respond with accelerated growth to recombinant growth hormone therapy in much the same way as do children with intrauterine growth retardation. Initiation of such therapy at a young age might significantly improve not only final

height, but developmental milestones as well. The discrepancy in head circumference in the very pre-term infant, although minimal, is nonetheless of considerable concern. Thus as the authors point out, it would be important to carefully record growth patterns, and developmental milestones over time in the attempt to define those children who might benefit most from earlier hormonal investigation and intervention. It would appear that the Swiss Minimal Neonatal Data Set is an excellent resource for the collection and analysis on such data.

William L. Clarke, MD

Adult Height in Advanced Puberty with or without Gonadotropin Hormone Releasing Hormone Analog Treatment

The authors define "advanced puberty" as "the onset of puberty in girls between 8 and 10 years and in boys between 9 and 11 years." (Others might also use the term "early puberty" for such subjects.) In a retrospective assessment of the effect of a gonadotropin releasing hormone agonist (GnRHa - D-Trp⁶-GnRH) upon adult stature in children with "advanced puberty," the authors administered GnRHa for 2-2.4 years to 9 adolescent girls with serum estradiol concentrations in excess of 20 pg/mL, and 8 pubertal boys with testosterone values greater than 100 ng/dL who had a pubertal gonadotropin secretory response to GnRH. Mean adult height of treated subjects was compared to that of a control group of untreated subjects. In treated girls, mean adult stature (155.3 cm) was insignificantly different from pretreatment predicted height (151.9 cm). In control females (N=31), mean adult and predicted heights were also similar (157 cm and 156.7 cm, respectively). In both groups, adult heights were close to their target heights. In treated boys, mean adult height (164.1 cm) was less than mean predicted height (173.2 cm) and mean target height (170.4 cm). In untreated boys (N=9), adult height, predicted, and target heights were similar (169.1, 170.8, and 170.2 cm, respectively). The authors concluded: "These data suggest that advanced puberty decreases the growth potential by about 5 cm, and that GnRHa treatment does not prevent this."

Couto-Silva AC, et al. *J Pediatr Endocrinol Metab* 2002;15:297-305.

Editor's Comment: Luckily, GnRHa did not increase adult stature in girls with "advanced puberty" and may even have led to decreased stature in boys. While under specific and individual circumstances (such as major behavioral problems, disabling physical handicaps, or significant developmental delay), one might consider interruption of pubertal development in subjects of normal adolescent age, to do so for the purpose of achieving a greater adult stature is an unjustified use of agents such as GnRHa. Similarly, the use of recombinant human growth hormone (rhGH) to increase to a minimal extent adult stature in normal but short children is unjustified medically, psychosocially, or financially.¹ Unfortunately, we may shortly expect to read a manuscript in which both GnRHa and rhGH have been administered to children with "advanced puberty."^{2,3} At what point did the pediatric endocrinologist cease being a physician-scientist and become a physician-cosmetologist?

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References

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2. Kamp GA, et al. *J Clin Endocrinol Metab* 2001;86:2969-2975.
3. Kaplowitz PB. *J Clin Endocrinol Metab* 2001;86:2965-2968.

GH Anabolic Effects of GC-Dependent Children with IBD

This pilot study utilizing 6 boys and 4 girls was designed to determine whether rhGH could overcome some of the catabolic effects of chronic glucocorticoid (CG) treatment (24 months) of IBD. Subcutaneous rhGH (0.05 mg/kg/d) was given for a minimum of 6 months. Seven patients continued for 12 months. Body composition

changed favorably with increased fat free mass and decreased fat mass. Linear growth velocity increased from 3.5 ± 0.4 cm/yr pre-rhGH to 7.7 ± 0.9 cm/yr after 6 months. The GV persisted for the next 6 months in all 7 treated. Bone calcium accretion increased as did alkaline phosphate specific for bone [(a measure of bone