

**Table. Significant risk factors in cancer survivors for the development of HI, IGT, or DM**

	Odds ratio (95% CI)	P value
BMT (54) vs. all others (158)	6.6 (3.1–13.9)	<0.001
ALL BMT (16) vs. no BMT (82) <sup>1</sup>	25.6 (6.6–100)	<0.001
TBI	13.8 (5.7–34.3)	<0.001
Pituitary irradiation (≥ 30 Gy)	4.5 (2.1–10.0)	<0.001
GH deficiency	5.1 (2.3–11.3)	<0.001
Untreated hypogonadism	21.1 (6.4–69.7)	<0.001
Untreated hypothyroidism	19.7 (2.1–181.2)	0.009
Overweight or obese (BMI)	5.3 (2.5–11.4)	<0.001
Abdominal adiposity <sup>2</sup>	14.5 (4.9–42.8)	<0.001
Family history of dyslipidemia	2.1 (1.0–4.2)	0.04
Hypertension	2.6 (1.1–5.8)	0.03
BMT survivors only (54)		
TBI	7.6 (2.2–26.2)	<0.001
Busulphan	0.2 (0.1–0.8)	0.02

<sup>1</sup> Patients with acute lymphoblastic leukemia (ALL) with and without BMT.

<sup>2</sup> Abdominal adiposity defined as a waist-to-height ratio more than 0.5.

(n)=number

Modified from Neville KA, et al. J Clin Endocrinol Metab. 2006;91:4401-7.

broad ranging diagnoses, and the grouping together of the 3 metabolic criteria. Interestingly, hypogonadism also emerged as an independent risk factor, and W/H ratio was a more important marker than BMI. In keeping with these data, it is suggested that the use of conditioning with TBI for BMT deserves reconsideration and underlines the need for regular and long-term clinical and metabolic follow-up.

Neville KA, Cohn RJ, Steinbeck KS, Johnston K, Walker JL. Hyperinsulinemia, impaired glucose tolerance, and diabetes mellitus in survivors of childhood cancer: prevalence and risk factors. J Clin Endocrinol Metab. 2006;91:4401-7.

**Editor's Comment:** Diabetes mellitus has not been considered a significant risk in the follow-up of cancer survivors. Initially, treatment with asparaginase suggested a rare immediate risk. Thereafter, the higher frequency of moderate—but significant—overweight observed in patients with leukemia suggested such a risk. In the present prospective study of a large group of etiologies, a new vision is emerging. Of note, some factors did not turn out to be significant: asparaginase-related hyperglycemia, diagnosis, small birth size, abdominal or testicular irradiation. The group at risk had BMT with TBI as conditioning, as opposed to busulfan conditioning, which had no significant effect on the metabolic outcome. The authors suggested that the pancreatic beta cell is an unlikely target, and instead focused on the effect of irradiation on the muscle mass by unknown mechanisms, one possibly being mitochondrial dysfunction. Little is known about the outcome of the irradiated adipose tissue and possible inflammatory processes.

This study provides some clinical clues such as early correction of hypogonadism and careful follow-up of W/H ratio. In the population at risk because of TBI, appropriate nutritional and lifestyle control may not be sufficient. More long-term studies are needed to help understand the mechanism(s) of these adipose—and possibly muscular—changes to help prevent metabolic syndrome and DM.

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## Reference

- Hoffmeister PA, Storer BE, Sanders JE. J Pediatr Hematol Oncol. 2004;26:81-90.

## Growth Attenuation in Developmental Disabilities

Caring for nonambulatory children with profound developmental and cognitive disabilities becomes more difficult as the child grows. Treatment with high-dose estrogen, can arrest further growth and facilitate the option of continued care in the home. This case report discusses medical and ethical considerations of such an intervention strategy and describes a comprehensive program including reviews by pediatric specialists in endocrinology, neurology, development, surgery, and ethics.

A 6-year, 7-month-old girl was referred to pediatric endocrinology for early pubertal development. She had a 1-year history of pubic hair and a 3-month history of breast budding. Static encephalopathy with marked global developmental deficits was previously diagnosed. Motor and cognitive development never progressed beyond that of an infant; at 6 years of age

she could not sit up, ambulate, or use language. She was gastrostomy-tube dependent for nutrition and responded to others by vocalizing and smiling. The consensus of the specialists was that there would be no significant future improvement in cognitive or neurological function.

The onset of puberty roused parental fears that they would not be able to continue to care for their daughter at home, despite their desire to do so, as she continued to grow. A plan to attenuate growth using high-dose estrogen was developed along with pretreatment hysterectomy. An institutional ethics committee met with the family, patient, and patient's physicians and reached consensus that requests for growth attenuation and hysterectomy were ethically appropriate in this case. Plans were instituted to convene an interdisciplinary review panel that included pediatric specialists in

endocrinology, neurology, development, surgery, and ethics. After an uneventful surgery and a little more than a year of daily transdermal estradiol (400 µg), the patient approached the end of her linear growth.

Gunther and Diekema reviewed the history of growth-attenuation therapy, in particular its application to tall adolescent girls. Most reported decreases in adult height between 2 cm and 10 cm, with greatest reductions observed the earlier the treatment was initiated. The authors speculated that “treatment beginning in a 5-year-old boy of average height and weight might result in a reduction in final length of as much as 24 inches (60 cm) and in weight of more than 100 pounds (45 kg).” What of the risks of treatment? Based on experiences in treating girls for constitutional tall stature, known short-term risks of high-dose estrogen treatment include mild nausea, headache, and weight gain. Long-term effects on fertility have recently been raised, although this risk did not apply to the case(s) in question. The effects of high-dose estrogen in young prepubertal children includes gynecomastia in boys, and rapid advancement of secondary sexual characteristics in girls, including uterine bleeding which can be controlled with injections of depot medroxyprogesterone acetate (DMPA) or hysterectomy. Concerns over the risk of thrombosis were not thought to be a reason to withhold this intervention. The authors acknowledged historical controversies associated with hysterectomy but, in profoundly impaired children, careful ethical and legal deliberations are needed.

Ethical factors in the decision to employ high-dose estrogen treatment to attenuate growth in a profoundly impaired individual included past abuses against this population justified by the benefits to society or the caretakers, rather than the individual. The authors discouraged overgeneralizing from past abuses directed toward mildly- to moderately-impaired individuals to the potential benefits of such interventions for those who are nonambulatory, profoundly cognitively and neurologically impaired, and wholly dependent on others for all their needs. Two major considerations in determining whether it is ethical to attenuate growth in this population exist: does growth attenuation offer the patient benefit, and does growth attenuation do any harm to the patient? A thoughtful discussion was presented with the thrust pointing in the direction of benefits to the child and family through the reduced physical burden on aging parents in attending to the changing physical needs of their child in the home. The authors addressed medical and psychosocial harm associated with this treatment, and concluded that patients such as the one being discussed would not be placed unduly at risk.

Gunther DF, Diekema DS. Attenuating growth in children with profound developmental disability: a new approach to an old dilemma. *Arch Pediatr Adolesc Med.* 2006;160:1013-17.

**Editor’s Comment:** *In an editorial accompanying this article, Brosco and Feudtner<sup>1</sup> acknowledged the*

*predicament facing parents of children with profound cognitive and physical disabilities who are considering continuing care in the home. In evaluating the reasoning of Gunther and Diekema’s strategy, they posed 4 questions: (1) Will early high-dose estrogen treatment enable such children to remain home under the care of their parents for longer periods of time? Will this improve the quality of their lives? What if the height-attenuated child continues to gain weight; wouldn’t this effect partially offset the benefits of shorter stature? These questions, in addition to concern over the association between low-dose estrogen therapy and seizures, lead the commentators to call for a rigorous investigation of assumptions underlying this intervention and examination of unforeseen risks; (2) Is it acceptable to manipulate a person’s height? Here, the authors have little trouble dispensing with such concerns; they opined that to not do so implies that a person’s value as a human being is dependent upon their physical size; (3) Will this treatment be misused? The history of the eugenic movement in the first half of the 20<sup>th</sup> century and more recent practices (eg, sterilization of individuals with mental retardation) that have come to be rejected, lead the authors to call for stiff safeguards and protections; and (4) Is the proposed treatment an attempt at a simple technical fix to a far more complex problem, that being the plight of families caring for such children without adequate societal support?*

*The authors concluded that attempts to attenuate growth in such cases are ill-advised. Instead, they claim what is needed are more funds for home-based services. They warn clinicians that adopting medical interventions, even in the context of interdisciplinary review with ethical oversight, will ultimately be judged “in the social-political context of both the disability rights movement and the woefully impoverished options for high-quality, long-term residential care of children or adults with profound developmental disabilities.”*

*Personally, I am particularly sympathetic to the fourth point of Brosco and Feudtner. It appears that in our effort to help struggling families, we may narrow our intervention options to those perceived to be in our control, in this case, high-dose estrogen therapy to attenuate growth. Adopting such an approach to achieve the desired outcome of allowing the parents to continue to care for their child at home seems far more attainable than trying to modify the state of home-based services. Besides, strictly speaking, we are not paid to do the latter. However, if there is validity to this line of reasoning, then how do we avoid choosing the expedient and readily available when it clashes with the just course of action?*

David E. Sandberg, PhD

## Reference

1. Brosco JP, Feudtner C. *Arch Pediatr Adolesc Med.* 2006;160:1077-8.