

# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## **Growth-Attenuation Therapy: Principles for Practice**

David B. Allen, Michael Kappy, Douglas Diekema and Norman Fost

*Pediatrics* 2009;123:1556-1561

DOI: 10.1542/peds.2008-2951

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/123/6/1556>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2009 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# Growth-Attenuation Therapy: Principles for Practice

David B. Allen, MD<sup>a</sup>, Michael Kappy, MD, PhD<sup>b</sup>, Douglas Diekema, MD, MPH<sup>c</sup>, Norman Fost, MD, MPH<sup>a</sup>

<sup>a</sup>Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; <sup>b</sup>Department of Pediatrics, University of Colorado School of Medicine, Denver, Colorado; <sup>c</sup>Department of Pediatrics, University of Washington School of Medicine, Seattle, Washington

The authors have indicated they have no financial relationships relevant to this article to disclose.

## ABSTRACT

Publication of an account of growth attenuation with high-dose estrogen in a child with profound physical and cognitive disability brought widespread attention to a common and complex issue faced by families caring for similarly affected children, namely, the potentially negative effect of the increasing size of a child on the ability of his or her family to provide independent care, which in turn makes it more difficult for parents to keep the child in the home and involved in family activities. In this article we explore the scientific rationale for, effectiveness and safety of, and ethical considerations bearing on growth-attenuation treatment of children with profound and permanent cognitive disability. Informed responses to key clinically relevant questions are proposed. Our analysis suggests that growth attenuation is an innovative and sufficiently safe therapy that offers the possibility of an improved quality of life for nonambulatory children with profound cognitive disability and their families. Pediatricians and other care providers should include discussion of these options as part of anticipatory guidance around the age of 3 years so that, if elected, potential clinically meaningful benefits of growth-attenuation therapy can be realized. Because of the publicity and debate surrounding the first reported case, ethics consultation is recommended. *Pediatrics* 2009;123:1556–1561

[www.pediatrics.org/cgi/doi/10.1542/peds.2008-2951](http://www.pediatrics.org/cgi/doi/10.1542/peds.2008-2951)

doi:10.1542/peds.2008-2951

### Key Words

growth, growth attenuation, cognitive disability, ethics

### Abbreviations

GnRH—gonadotropin-releasing hormone  
ER—estrogen receptor

Accepted for publication Oct 28, 2008

Address correspondence to David B. Allen, MD, University of Wisconsin American Family Children's Hospital, University of Wisconsin School of Medicine and Public Health, H4/448 CSC-Pediatrics, 600 Highland Ave, Madison, WI 53792-4108. E-mail: [dballen@wisc.edu](mailto:dballen@wisc.edu).

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2009 by the American Academy of Pediatrics

**I**N 2006, PUBLICATION of an account of growth attenuation with high-dose estrogen in a child with profound cognitive disability<sup>1</sup> brought widespread attention to a common and complex issue faced by families caring for a child with profound cognitive disability, namely, the potentially negative effect of the child's increasing size on a family's ability to provide independent care, which in turn makes it more difficult for the parents to keep the child in the home and involved in family activities. In this case, the family's assertion that smaller size would improve their child's quality of life led to hormonal intervention therapy to hasten and prematurely curtail linear growth. The ensuing media publicity, controversy, and debate revealed a high degree of sympathy and shared interest from many families in similar situations but also led other families, health care providers, and interested and invested parties to express concerns that such treatment was unethical. In addition, a recent informal survey of pediatricians and pediatric endocrinologists at a 2008 Pediatric Academic Society symposium on growth attenuation indicated that a high proportion of endocrinologists had been confronted with this clinical dilemma, many had already been asked to provide growth-attenuation treatment, and a careful and balanced analysis leading to practical clinical, ethical, and logistic guidelines would be helpful.

In this article we explore the scientific rationale for, effectiveness of, and ethical considerations bearing on growth-attenuation treatment of children with profound and permanent cognitive disability. The objective is to develop informed responses to the following clinically relevant questions: (1) What information would accurately describe the likely benefits and risks of estrogen growth-attenuation therapy? (2) In what ways should potential benefits of growth attenuation influence the approach to treatment (or nontreatment) of precocious puberty in these children? (3) Should families caring for such a child be informed in early childhood about the possibility of growth attenuation? (4) Should requests for growth-attenuation therapy to improve quality of life be given the same respect as is currently accorded to requests for growth-promoting therapy? and (5) What is the role for ethics committee and/or legal review in the administration of growth-attenuation therapy? The original case report by Gunther and Diekema,<sup>1</sup> a case subsequently identified as a young girl named Ashley, included an elective hysterectomy and removal of the child's breast buds. Although these 2 procedures undoubtedly added to the publicity and controversy surrounding the case, neither of them would be essential accompaniments of growth-attenuation therapy. In this article, we limit our discussion to growth attenuation.

Although we recognize that there is no precise definition of profound cognitive disability and cognitive disability exists on a continuum, for purposes of growth-attenuation therapy we define profound cognitive disability as including nonambulation and requiring assistance with nearly every aspect of daily living, remaining completely dependent on others for even basic care even after careful attempts at training, and the inability to understand or express oneself in nuanced ways. There should be a reasonable assumption of permanency on the basis of careful

clinical evaluation by a pediatrician who is experienced in working with children with severe and profound cognitive disability.

Some will wonder how one can know the extent to which a child with profound cognitive disability understands his or her own condition or the impact of medical decisions made on his or her behalf. Although we have suggested a definition of profound cognitive disability, ascertainment of whether a person meets this definition is a separate issue. Ascertainment of subjective states is always imperfect, especially in pediatrics and especially in children with profound cognitive disabilities. Uncertainty is inherent in medicine, and one must proceed on the basis of the most likely facts.

It is also important to distinguish theoretical uncertainty from actual uncertainty. In the case of Ashley, there was little doubt that she meets the criteria. Moreover, doing "nothing" in the situations under discussion cannot be assumed to lead to the best outcomes for these children. As is always the case in medicine, physicians and parents must proceed on the basis of their best assessment of the likely facts and outcomes.

### MEDICAL ISSUES/CONSIDERATIONS

Growth attenuation using estrogen causes skeletal maturation to occur early and at an accelerated tempo, thereby limiting the linear growth achieved before growth-plate closure. Clinical and experimental observations have illustrated that early exposure to estrogen is a potent growth-attenuating event.<sup>2</sup> Children with naturally occurring and untreated early estrogen excess caused by central or peripheral precocious puberty show growth-rate acceleration, with rapid bone age advancement, early cessation of growth, and eventual short stature. Alternatively, suppression of either central precocious puberty with gonadotropin-releasing hormone (GnRH) analog therapy, reduction of estrogen production by aromatase inhibition,<sup>3</sup> or antagonism of estrogen effect with estrogen receptor (ER) blockade can slow skeletal maturation, extend the growth period, and increase height. In vitro experiments have demonstrated ERs in growth-plate cartilage, with relative influence of ER- $\alpha$  (growth-stimulating) and ER- $\beta$  (growth-inhibiting) receptor effects being influenced by age, gender, and estrogen concentration. Low concentrations of estrogen enhance chondrocyte growth, whereas high concentrations inhibit cartilage cell division and promote maturation and senescence of chondrocytes.<sup>4</sup> The central role for estrogen (as opposed to androgens) in the growth-plate-maturation process was illustrated by case reports of male subjects in their mid-20s with either decreased estrogen synthesis (aromatase deficiency)<sup>5</sup> or action (ER defect)<sup>6</sup> who were experiencing prolonged linear growth and marked delays in skeletal maturation.

Because of its ability to advance skeletal maturation in excess of normal height-age increases, estrogen has been used as a growth-attenuating agent in females for whom the prospect for excess height was viewed as a disability, particularly during the 1950s, 1960s, and 1970s.<sup>7</sup> During the past 30 years, increased social acceptance of tall stature in females and the greater visibility

of positive female role models who are tall have markedly reduced requests for such treatment, and the criteria for initiation of growth-attenuation therapy have changed accordingly<sup>8</sup>; in a 1978 survey of US pediatric endocrinologists, 25% reported that they would initiate treatment for a predicted height of 6 feet, whereas in 2002 only 5% said they would do so. Treatment regimens have typically relied on oral administration of estradiol (2.5–20 mg/day) or ethinyl estradiol (0.05–0.3 mg/day). It has been estimated that the ratio of bone-age to height-age advancement during estrogen treatment is between 2.0 and 3.7.<sup>9</sup> However, reported decrements in height have been relatively modest; in a survey of pediatric endocrinologists, 94% of the respondents reported a height reduction of between 2 and 7 cm, and only 6% of the respondents reported reductions of >7 cm. Effect size is affected most profoundly by the timing of treatment, with height-reduction effect being inversely proportional to bone age at the start of estrogen exposure. Higher dosage and oral (versus transdermal) route of administration are other factors that are likely to result in a greater response, but the relative magnitudes of these 2 factors have not been well described. Analysis of pooled data from several studies predict a growth-attenuating effect of  $6 \pm 1.5$  cm at a bone age of 10 years,  $3 \pm 1.0$  cm at a bone age of 12 years, and no effect at a bone age of 14 years.<sup>10</sup> Whether the slope of this regression line can be extrapolated to initiation of treatment at much younger bone ages is not known, but on the basis of height outcomes of children with naturally occurring untreated precocious puberty, it is reasonable to expect a potential growth attenuating effect significantly >6 cm.

Information regarding growth-attenuation treatment is not available for boys. Early-life spontaneous precocious puberty in males, associated with exposure to both testosterone and (through aromatization) estrogen, is associated with significant ultimate height reduction. However, the greater growth-promoting effects of testosterone compared with estrogen (alone) suggest that administration of exogenous testosterone would be less effective in attenuating linear growth than estrogen. In addition, other anabolic effects of testosterone would likely accelerate weight gain more than estrogen. It would then seem reasonable to consider estrogen the currently preferred agent for growth attenuation in both boys and girls. Breast-bud removal in males should be considered as a reasonable corollary to treatment.

Mild adverse effects such as nausea, areolar hyperpigmentation, breakthrough bleeding, and weight gain are common but are usually transient and rarely require interruption of therapy.<sup>11</sup> The feared theoretical complication of venous thrombosis is extremely rare, reported in only 2 of 1374 pediatric/adolescent cases.<sup>12</sup> Concerns have also been raised about decreased fertility (which should not be an issue for a child with profound cognitive disability) and future malignancy. Although early studies of early estrogen exposure suggested a possible increase in risk for breast and uterine cancer,<sup>13</sup> more recent analyses have suggested no such adverse effects.<sup>14,15</sup> In summary, current information suggests that adverse effects are not a significant factor in the decision

to recommend or not recommend growth-attenuating therapy. However, it is important to note that (1) these risk estimates are based on data from clinical studies of similar but distinct (eg, precocious puberty and treatment of tall females) clinical situations, and (2) no information regarding the safety of estrogen administration to males is available.

Three practical points deserve special attention for growth-attenuation treatment of children with profound cognitive disabilities. First, prediction of height potential (and, therefore, treatment effect) is problematic. Even for children without disabilities, the 2-SD range for predicted heights based on either bone-age-maturation formulae or parental heights is approximately +10 cm, indicating that, in the best of circumstances, height predictions at an early age are broad approximations.<sup>16</sup> Without any intervention, children with this degree of disability rarely attain an ultimate length commensurate with predicted height based on either mid-parental-height or bone-age projections. In addition, the relationship between bone-age assessment, actual linear growth potential, and timing of pubertal onset is often disrupted by mineralization defects caused by immobilization or metabolic and nutritional factors. Increases in length are often compromised by scoliosis and contractures. Although these factors would not be expected to eliminate a growth-attenuating effect of premature estrogen exposure, they make accurate predictions of height reduction difficult. Second, for purposes of ease of mobility and care, the more important size-reduction parameter is weight, not height. Thus, predictions for and realization of “ease-of-care benefit” resulting from growth attenuation assumes that weight reduction will be commensurate with length reduction. To be effective, decisions to limit linear growth should be matched by commitment to limit calories sufficiently to maintain a relatively lean body habitus. Third, children with profound central nervous system disabilities are at significantly increased risk for demonstrating endogenous central precocious puberty as a result of damage of normal inhibitory neural pathways. Currently, typical treatment of precocious puberty includes GnRH analog suppression of central puberty, primarily to avoid premature physical development and, in females, early onset of menses. In contrast, the possible benefits of growth attenuation would mean that nontreatment, or even acceleration of the pubertal process through the use of exogenous estrogen, should now be considered as a therapeutic alternative with long-term ease-of-care benefits that might outweigh the shorter-term advantages of suppressing pubertal progression.

### **ETHICAL CONSIDERATIONS**

Many of the concerns expressed about the treatment of Ashley<sup>1</sup> were related to the hysterectomy and removal of her breast buds.<sup>17,18</sup> We focus here on the concerns directed at growth attenuation. Our purpose is to suggest general principles that will help parents and providers anticipate and respond to concerns raised by colleagues, ethics committees, or outside critics.

### **The Treatment Is Experimental and Has Unknown Benefits and Risks<sup>19</sup>**

All clinical interventions are experimental in the sense that they start with a hypothesis, an uncertain outcome, and a “clinical trial,” resulting in continuing assessment and consideration of alternative hypotheses and trials.<sup>20</sup> Although some pediatric interventions have been subjected to well-designed clinical trials, an estimated 80% of pediatric prescriptions involve drugs that have never been tested for safety or efficacy in the treated age group.<sup>21</sup> Estrogen therapy for growth attenuation is within this broad category of “innovative therapy” or off-label use of approved drugs. As noted, the safety profile of estrogen in children is reasonably well established, and the risks are likely to be extremely low. The benefits, as measured by final adult height and weight, are uncertain, but it is highly likely that there would be measurable attenuation if treatment were started at an early age.

If the “experimentation” charge is meant to imply that growth-attenuation therapy in this group of children necessarily has research intent, requiring review by an institutional review board, there is no basis for such a claim. It would be desirable, however, if future cases were part of a larger study or at least included in a registry, which would require institutional review board review.

### **The Parents’ Motives Are Selfish; the Treatment Is Designed to Advance Their Interests, Not the Patient’s Interests**

Here again there is no evidence for the claim. By all accounts, most parents are extraordinarily committed to the welfare of their profoundly disabled child. That being said, the interests of parents and child are likely to be congruent in the case of growth attenuation, not in conflict. Although a smaller child would be beneficial for the parents, if growth attenuation achieves the purpose of increasing the child’s access to experiences that seem to be enjoyed, increases the duration of care in the home, and reduces the risk of bedsores, then the treatment may be serving the interests of the whole family, including the child.

Apart from these empiric arguments, judging parental motives is complex. Acknowledging the intertwining of interests of these dependent children and their families, some would argue that family care providers themselves have legitimate and justifiable interests at stake (eg, parents with weakness or arthritis could legitimately want a smaller child for ease of care).<sup>22</sup> In addition, parents’ motives can be conceptually unrelated to the question of whether a proposed treatment is in the child’s interests.<sup>23</sup> If, for example, parents agree to an appendectomy for a child with appendicitis but with a bizarre evil intent (eg, hoping the child will die), their motive would be irrelevant in deciding whether surgery would be in the child’s interest.

### **Disability Is Socially Determined; the Environment Should Be Changed, Not the Patient’s Body**

Disability rights groups justifiably assert that disability results from an interaction between an individual and his or her environment and that changes in the envi-

ronment should be preferred to manipulations of the patient's body.<sup>19,24,25</sup> Legislative successes have produced important environmental changes, such as use of ramps, wheelchair-accessible buses, and talking computers for blind persons. That said, it remains the case that sometimes bodily changes, including those resulting from invasive surgery, is the best option for an individual (eg, a child with severe scoliosis or club feet), and in some cases a combination of environmental and bodily changes will maximize an individual's opportunities.

Critics of growth-attenuation treatment point out that mechanical lifts and motorized vehicles can mitigate the burdens of body mass. However, these technologies are not universally available or affordable, and they cannot be available in all places at all times. Parents of profoundly disabled children commonly describe a tipping point when the child becomes too big or heavy to conveniently move at will. A smaller, lighter person is easier to move than a heavier one, and if the difference is large enough, the quality of the patient's life may be affected. Although such a threshold is arbitrarily defined depending on the size, strength, and physical agility of care providers, personal communications from families suggest that a weight of <60 pounds (~27 kg) and length of 4 ft 6 in (~137 cm) is desirable.

#### **Growth Attenuation Freezes the Person as a Child, Interferes With His or Her Right to Become an Adult, and Undermines His or Her Dignity**

Estrogen-induced growth attenuation does not interfere with other aspects of the aging process. For instance, Ashley (11 years old at this writing) will age as she would have and will acquire the appearance of an adult, albeit a very short adult. Because she will rarely be seen outside of a bed or chair, her short stature will not be noticed by most, nor will she have the subjective experiences of whatever stigma may attach to short stature. Effects of short stature on access to jobs, mates, sports, or cars will be of no consequence to her. The typical advantages of being an adult, rather than a child (autonomy, work, marriage, procreation, etc), also have no meaning for her.

The claim that growth attenuation would strip the treated child of his or her dignity is difficult to understand absent some specificity about the meaning of the term in this context. In other contexts, "dignity" refers to other interests such as autonomy or embarrassment. However, often it is used without any definition, leading some to consider it a "useless concept"<sup>26</sup> absent a specific explanation of its meaning in a specific setting.

#### **Growth Attenuation of Children With Profound Cognitive Disability Is the Beginning of a Slippery Slope; Strict Social Controls Are Needed to Prevent a Rapid Descent**

All technologies entail risks and all can be misused. This is not just hypothetical; most biomedical technologies have been misused, sometimes with catastrophic results including deaths of patients from nonindicated toxic treatments, risks to future generations from overuse of broad-spectrum antibiotics, or profound economic ef-

fects from inappropriate expenditures. If this is what is meant by a slippery slope, it is a useful metaphor to encourage caution in the use of expansive biotechnologies, well-designed studies to clarify likely benefits and risks, and sometimes regulations to limit or even prohibit the use of technologies that have been found over time to carry an unacceptable risk/benefit ratio.

In the Ashley case, a disability rights group persuaded the Seattle Children's Hospital to agree that they would never begin such treatment without review by a court.<sup>27</sup> Apart from political considerations, it is difficult to discern a principled basis for such an extraordinary restriction for a treatment that incurs such low medical risk. Court review has often been sought for withholding or withdrawing life-sustaining treatments but rarely, if ever, for permission to begin a treatment, particularly a minimally invasive treatment.

The concerns about adverse psychosocial effects of growth attenuation would arise if the treatment were applied to a child who was more developmentally advanced than in the definition of severe cognitive disability we offered above. Excessive short stature could obviously be physically, emotionally, and socially disabling for a child with clearer opportunities for social interaction. Therefore, it is appropriate to limit such treatment at the present time to children with such profound cognitive disability that short stature would clearly not be accompanied by any loss of social or physical experiences or negative impact on self-image.

Although previous permission by a court is virtually unknown for low-risk medical treatments, a more common process for complex and controversial medical decisions is review by a hospital ethics committee. This was done in Ashley's case, with unanimous support for the parent's request. One purpose of such review would be to ensure that candidates have been thoroughly evaluated and that treatment decisions are based on the best available medical facts and a thorough consideration of the ethical concerns raised by critics of the procedure. Ethics committee review can also serve to protect an institution, physician, or family from a charge that they embarked on an innovative treatment plan without careful consideration of the relevant facts and ethical considerations.

Critics of mandatory ethics committee review correctly point out that many more difficult decisions, with life-and-death consequences, are routinely made on a daily basis throughout the country without previous review by an ethics committee. It may also be that the controversy surrounding Ashley was exacerbated by the hysterectomy and the unusual procedure of removing her breast buds to prevent anticipated complications of large breasts. New ideas and practices commonly evoke uneasiness and concern. Growth attenuation may become as common as growth promotion, or it may fail to achieve the desired results and, like many new ideas, fade into history.

#### **PRINCIPLES FOR GROWTH ATTENUATION IN PRACTICE**

1. Consideration of growth-attenuation therapy should be restricted to nonambulatory children with a diag-

nosis of profound cognitive disability, confirmed by a physician who is experienced in the assessment of children with cognitive disability, with a near certain prognosis for no significant improvement in cognitive function. Children who are aware of their social environment or who have the capacity for social achievement may suffer from the stigmatization that often accompanies extreme short stature.

2. Growth-attenuation therapy should be given equal respect with growth-promoting therapy. Many medical and surgical interventions permanently change the appearance of a patient. The justification should always be based on a careful assessment of the likely benefits and risks, both medical and psychosocial, with the interests of the child being the focus.

Strong similarities between interests of the child and family pursuing either growth-enhancement or growth-attenuation therapy suggest that the respect for either "growth-altering" therapy should be equal. Growth-enhancement therapy for quality-of-life purposes in children without growth-hormone deficiency is well established and accepted by the medical community, the US Food and Drug Administration, and most third-party payers. In these situations, providers generally accept and trust the motives of parental advocacy for their child's quality-of-life interests when height augmentation is the goal. When there is doubt or disagreement about whether a proposed intervention is in the best interests of the child, review by an ethics committee should be sought.

3. Families caring for a child with profound cognitive disability should be informed in early childhood about the possibility of growth attenuation. Smaller size can represent a quality-of-life benefit for children with disabilities that are so profound that the child's personal care and interaction with the environment is totally dependent on the care provided by others. Because the clinical effectiveness of estrogen-induced growth attenuation is inversely related to age at initiation, opportunity for therapeutic consideration should occur early enough to achieve the intended biological effect. Although it may be reasonable to adjust timing of therapy on the basis of growth predictions that exceed a target threshold (eg, 4 ft 6 in, so that children with a larger size prognosis would be candidates for the earliest treatment), pitfalls in the accuracy of linear growth prediction suggest that a general earlier-treatment-is-more-effective approach is more practical.

There is not yet sufficient information to justify recommending growth attenuation as a routine treatment, but the low likelihood of serious harm and reasonable prospects for benefit justify inclusion in a list of optional interventions for such children. Most parents will be unaware of this possibility, so care providers should bring it to their attention in as neutral a way as possible, with candid review of the likely benefits, risks, and alternatives. Interested parents should be referred to responsible articles for and against growth attenuation.

4. Although a qualitative and favorable description of risks versus benefits can be provided, informed consent must acknowledge uncertainty with regard to both the prediction of long-term risks and the magnitude of growth-attenuating benefit. Risks of estrogen growth-attenuation therapy seem small, but this conclusion derives from studies of children with precocious puberty and tall stature treated with estrogen. Families must know that long-term adverse effects of short-term high-dose oral estrogen treatment in very young children, although unlikely, have not been well studied. With regard to therapeutic efficacy, estrogen administration will reduce linear growth, with the greatest effect occurring with initiation at a young bone age. High dosage and oral administration will likely further enhance that effect. The hoped-for clinical effect (ie, increased ease of handling) requires success in restraining weight gain as well as linear growth.
5. Potential benefits of growth attenuation should add a new dimension to choices of management of precocious puberty in children with profound cognitive disabilities. In children with profound cognitive disabilities, concerns regarding early pubertal maturation and, in females, the onset of menses commonly prompt initiation of puberty-suppression therapy with GnRH analogs. Advantages of early growth cessation and smaller size, on the other hand, suggest that parents should be informed that an "adverse effect" of this intervention is a prolonged growth period and its associated increase in ultimate height and that potential beneficial growth-attenuating effects of nontreatment (or depot-progesterone and estrogen to eliminate menses) should be given consideration as an alternative treatment.
6. Review by an institutional ethics committee should be considered in all cases until more data are available on outcomes and is strongly recommended if there is disagreement or doubt about whether such treatment is in the best interests of the child. Previous review by a court is inappropriate. The extraordinary publicity surrounding growth-attenuation therapy has made many physicians and hospitals cautious about offering such treatment. Although ethics committee review is rarely required, and extraordinarily uncommon for low-risk interventions including numerous unproven innovative therapies, the risk of outside criticism makes it prudent to have independent review of cases under consideration.

Review by an ethics committee, or an individual bioethicist, is common when there is disagreement among family members, among care providers, or between the family and the care providers. This principle should apply to cases of growth attenuation as well. The requirement for court review imposed on Seattle Children's Hospital had no legal basis and is inconsistent with standards of medical practice. Previous approval of a court, or court-appointed guardian, for treatment decisions of a child is generally restricted to cases that meet statutory

standards of child abuse or neglect or to cases in which a child is placed at substantial risk of serious harm by parents who refuse standard-of-care treatment recommended by the child's physician.

7. Ideally, growth-attenuation therapy should be part of a research protocol. It is not possible to require that all innovative therapies be provided only in a research context. Such a requirement could lead to a cessation of an estimated 70% to 80% of current pediatric treatments.<sup>21</sup> It would be very difficult to conduct a prospective randomized, controlled trial of growth attenuation; the number of cases for each participating center is likely to be very small, and there are too many uncontrollable clinical variables. That said, it should be feasible to develop a registry of those both choosing and declining treatment, with appropriate safeguards of confidentiality. Such a registry would allow some comparison of outcomes, tracking of adverse events, sharing of experiences, and greater awareness of the potential value of growth-attenuation therapy.

## CONCLUSIONS

Growth attenuation is an innovative therapy that offers the possibility of an improved quality of life for children with profound cognitive disability and their families. It can be achieved by allowing natural precocious puberty to run its course or by providing 1 to 4 years of exogenous estrogen orally or by transdermal patch. The risks of exogenous estrogen are likely to be low. Pediatricians and other care providers should include discussion of these options as part of anticipatory guidance at approximately the age of 3 years so that the potential benefits can be maximized. Ethics consultation is recommended because of the unusual publicity surrounding the first reported case.

## REFERENCES

1. Gunther DF, Diekema D. Attenuating growth in children with profound developmental disability: a new approach to an old dilemma. *Arch Pediatr Adolesc Med.* 2006;160(10):1013–1017
2. Nilsson O, Marino R, De Luca F, Phillip M, Baron J. Endocrine regulation of the growth plate. *Horm Res.* 2005;64(4):157–165
3. Laue L, Kenigsberg D, Pescovitz OH, et al. Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med.* 1989;320(8):496–502
4. Takano H, Aizawa T, Irie T, Itoi E, Kokubun S, Roach HI. Normal bone growth requires optimal estrogen levels: negative effects of both high and low dose estrogen on the number of growth plate chondrocytes. *Tohoku J Exp Med.* 2008;214(3):269–280
5. Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. *J Clin Endocrinol Metab.* 1995;80(12):3689–3698
6. Smith EP, Boyd J, Frank GR, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man [pub-

- lished correction appears in *N Engl J Med.* 1995;332(2):131]. *N Engl J Med.* 1994;331(16):1056–1061
7. Drop SL, De Waal WJ, De Muinck Keizer-Schrama SM. Sex steroid treatment of constitutionally tall stature. *Endocr Rev.* 1998;19(5):540–558
  8. Lee JM, Howell JD. Tall girls: the social shaping of a medical therapy. *Arch Pediatr Adolesc Med.* 2006;160(10):1035–1039
  9. Bierich JR. Estrogen treatment of girls with constitutional tall stature. *Pediatrics.* 1978;62(6 pt 2):1196–1201
  10. Venn A, Epid GD, Hosmer T, et al. Oestrogen treatment for tall stature in girls: estimating the effect on height and the error in height prediction. *Clin Endocrinol (Oxf).* 2008;68(6):926–929
  11. Barnard ND, Scialli AR, Bobela S. The current use of estrogens for growth-suppressant therapy in adolescent girls. *J Pediatr Adolesc Gynecol.* 2002;15(1):23–26
  12. Conte FA, Grumbach MM. Estrogen use in children and adolescents: a survey. *Pediatrics.* 1978;62(6 pt 2):1091–1097
  13. Mack TM. Postmenopausal carcinoma as a result of estrogen treatment: survey of evidence. *Pediatrics.* 1978;62(6 pt 2):1104–1113
  14. de Waal WJ, Torn M, de Muinck Keizer-Schrama SM, Aarsen RS, Drop SL. Long term sequelae of sex steroid treatment in the management of constitutionally tall stature. *Arch Dis Child.* 1995;73(4):311–315
  15. Hamilton AS, Mack TM. Puberty and genetic susceptibility to breast cancer in a case-control study in twins. *N Engl J Med.* 2003;348(23):2313–2322
  16. Allen DB, Rose SR, Reither EO. Normal growth and growth disorders. In: Kappy MS, Allen DB, Geffner ME, eds. *Principles and Practice of Pediatric Endocrinology.* Springfield, IL: Charles Thomas; 2005:77–203
  17. Coleman G. The irreversible disabling of a child: the "Ashley treatment." *Natl Cathol Bioeth Q.* 2007;7(4):711–728
  18. Ouellette AR. Growth attenuation, parental choice, and the rights of disabled children: lessons from the Ashley X case. Available at: <http://ssrn.com/abstract=1084903>. Accessed August 29, 2008
  19. Brosco JP, Feudtner C. Growth attenuation: a diminutive solution to a daunting problem. *Arch Pediatr Adolesc Med.* 2006;160(10):1077–1078
  20. Fost N. Ethical dilemmas in medical innovation and research: distinguishing experimentation from practice. *Semin Perinatol.* 1998; 22(3):223–232
  21. Roberts R, Rodriguez W, Murphy D, Crescenzi T. Pediatric drug labeling: improving the safety and efficacy of pediatric therapies. *JAMA.* 2003;290(7):905–911
  22. Lindemann H, Nelson JL. The romance of the family. *Hastings Cent Rep.* 2008;38(4):19–21
  23. Savalescu J. The proper place of values in the delivery of medicine. *Am J Bioeth.* 2007;7(12):21–22; discussion W1–W2
  24. Disability Rights Education and Defense Fund. Modify the system, not the person. Available at: <http://dredf.org/news/ashley.shtml>. Accessed August 29, 2008
  25. Ellis EB. Disabling children with disabilities. *Arch Pediatr Adolesc Med.* 2007;161(4):419
  26. Macklin R. Dignity is a useless concept. *BMJ.* 2003;327(7429):1419–1420
  27. Washington Protection and Advocacy System. "Ashley treatment" investigation. Available at: [www.disabilityrightswa.org/news-1/ashley-treatment-investigation](http://www.disabilityrightswa.org/news-1/ashley-treatment-investigation). Accessed August 29, 2008

**Growth-Attenuation Therapy: Principles for Practice**  
David B. Allen, Michael Kappy, Douglas Diekema and Norman Fost  
*Pediatrics* 2009;123;1556-1561  
DOI: 10.1542/peds.2008-2951

<b>Updated Information &amp; Services</b>	including high-resolution figures, can be found at: <a href="http://www.pediatrics.org/cgi/content/full/123/6/1556">http://www.pediatrics.org/cgi/content/full/123/6/1556</a>
<b>References</b>	This article cites 23 articles, 15 of which you can access for free at: <a href="http://www.pediatrics.org/cgi/content/full/123/6/1556#BIBL">http://www.pediatrics.org/cgi/content/full/123/6/1556#BIBL</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>Adolescent Medicine</b> <a href="http://www.pediatrics.org/cgi/collection/adolescent_medicine">http://www.pediatrics.org/cgi/collection/adolescent_medicine</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.pediatrics.org/misc/Permissions.shtml">http://www.pediatrics.org/misc/Permissions.shtml</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://www.pediatrics.org/misc/reprints.shtml">http://www.pediatrics.org/misc/reprints.shtml</a>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

