Attenuating Growth in Children With Profound Developmental Disability

A New Approach to an Old Dilemma

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C aring for children with profound developmental disabilities can be difficult and demanding. For nonambulatory children with severe, combined neurologic and cognitive impairment, all the necessities of life must be provided by caregivers, usually parents, and these tasks become more difficult as the child grows to adolescence and adulthood. Many parents would like to continue caring for their child with special needs at home but find it difficult to do so as the child increases in size. If growth could be permanently arrested while the child was still small, both child and parent would likely benefit because this would facilitate the option of continued care in the home. Treatment of the child with high-dose estrogen, initiated at an early age, could provide this option. High-dose estrogen both inhibits growth and rapidly advances maturation of the epiphyseal growth plates, bringing about permanent attenuation in size after a relatively short period of treatment. We present a case report and discuss the medical and ethical considerations of such an intervention strategy. We suggest that after proper screening and informed consent, growth-attenuation therapy should be a therapeutic option available to these children should their parents request it.   *Arch Pediatr Adolesc Med. 2006;160:1013-1017*

The American Academy of Pediatrics recently endorsed the goal of *Healthy People 2010* to reduce the number of children and youth with disabilities in congregate care facilities to zero by the year 2010.[1] The American Academy of Pediatrics Committee/Section on Children With Disabilities notes that "most parents desire to raise their children with special health care needs at home"[1(p507)] and supports a shifting emphasis away from placement strategies to permanency planning in the "belief that all children, regardless of the presence of a disability, belong in families."[1(p508)]

However, caring for a nonambulatory child with severe, combined developmental and cognitive disabilities can be a daunting task for parents, especially as the child increases in size.[2] The difficulties of caring for these children—dressing, bathing, diapering, transferring from bed to wheelchair, transporting—increase exponentially as the children grow to adolescence and adulthood. Despite medical and technological advances, many parents who would like to continue caring for their child with special needs at home find it difficult to do so given the physical limitations imposed by continued growth. Achieving permanent growth attenuation while the child is still young and of manageable size would remove one of the major obstacles to family care and might extend the time that parents with the ability, resources, and inclination to care for their child at home might be able to do so.

For editorial comment see page 1077

Treatment with high-dose estrogen could accomplish this goal. In high doses, estrogen both arrests growth and rapidly advances maturation of the epiphyseal growth plates. This combined effect should bring about permanent attenuation in size after a relatively short period of treatment.

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At our institution, we have begun such a treatment protocol in a child who meets the criteria for severe, irreversible neurologic and cognitive impairment. The treatment was requested by the parents and initiated after careful consultation and review by our institutional ethics committee. Other children are being considered for treatment as part of a comprehensive program that includes review by pediatric specialists in endocrinology, neurology, development, surgery, and ethics.

In this article, we present the child's case, discuss the history of growth-attenuation therapy, and make an argument for the careful application of such a treatment strategy in nonambulatory, profoundly impaired children. We believe that foreshortening growth in these children could result in a positive benefit in the quality of life for both child and caregiver, and we propose that in situations in which parents request such an intervention, it is both medically feasible and ethically defensible.

CASE REPORT

The patient is a 6-year-7-month-old white female initially referred to the pediatric endocrine service for early pubertal development. She had been the full-term product of an unremarkable pregnancy followed by an uncomplicated birth. After the first month of life, she began to display symptoms of hypotonia, feeding difficulties, choreoathetoid movements, and developmental delay. Extensive subsequent evaluation by specialists in neurology, medical genetics, and developmental pediatrics failed to uncover a specific cause. Static encephalopathy with marked global developmental deficits eventually was diagnosed. In the ensuing years, her development never progressed beyond that of an infant. At the age of 6 years, she cannot sit up, ambulate, or use language. She is gastrostomy-tube dependent for nutrition. However, she clearly responds to others—vocalizing and smiling in response to care and affection. The combined opinion of the specialists involved in her care is that there will be no significant future improvement in her cognitive or neurologic baseline.

Since birth, the patient has been cared for in the home by her parents, both of whom are college-educated professionals. She has 2 healthy siblings. Despite her severe disability, she clearly is an integral, and much loved, member of the family.

The patient presented for endocrine evaluation with a 1-year history of pubic hair development and 3-month history of breast budding. The parents were particularly concerned about accelerated growth, the patient having advanced from the 50th to the 75th percentile for length during the previous 6 months. After some probing, it was clear that the onset of puberty had awakened parental fears for their daughter's long-term future. The parents particularly feared that continued growth eventually would make it untenable for them to care for their daughter at home, despite their strong desire to do so. They were concerned that care might eventually have to be "put in the hands of strangers." There were also concerns about the complications of puberty, particularly the onset of menses.

After extensive consultation between parents and physician, a plan was devised to attenuate growth by using high-dose estrogen and to reduce the long-term complications of puberty in general, and treatment adverse effects in particular, by performing pretreatment hysterectomy. Because a growth-attenuating treatment regimen is unconventional, and bound to be controversial, the case was referred to our institutional ethics committee. The committee met with the family, the patient, and the patient's physicians and carefully explored the family's reasons for their request. After a lengthy discussion, the committee reached consensus that both the requests for growth attenuation and hysterectomy were ethically appropriate in this case. The committee also recognized that, although justified in this patient, growth attenuation should be considered in future patients only after careful evaluation of the risks and benefits on a case-by-case basis. Toward that end, plans were instituted to convene an interdisciplinary review panel that includes pediatric specialists in endocrinology, neurology, development, surgery, and ethics.

After uneventful surgery, the patient began a course of 400 μg of transdermal estradiol daily. She is followed up every 3 months and carefully monitored for growth, bone age, insulin-like growth factor I, estrogen and prolactin levels, and thrombotic factors. She is now a little more than a year into therapy and approaching the end of her growth. As of yet, there have been no treatment complications.

THE HISTORY OF GROWTH-ATTENUATION THERAPY

Physicians long have appreciated that one consequence of early puberty is its deleterious effect on growth. In children who are exposed to sex steroids prematurely, final adult height is seriously attenuated because of acceleration in epiphyseal (growth plate) maturation.[3] The earlier the onset of puberty, the greater the reduction in final height.[4] Although both estrogens and androgens accelerate growth, it is now appreciated that estrogen is the dominant hormone in the advancement of skeletal maturation in both boys and girls and seems exclusively responsible for bringing about epiphyseal fusion and an end to growth.[5]

The effect of estrogen on growth appears to be biphasic. Although physiologic levels of estrogen accelerate growth (the pubertal growth spurt), supraphysiologic doses paradoxically tend to inhibit growth.[4,6,7] The mechanism by which high levels of estrogen interfere with growth is not completely understood but may be caused, at least in part, by estrogen's suppression of insulin-like growth factor I (or somatomedin C), the peptide that mediates the growth-promoting effects of growth hormone.[8-10]

It is not surprising that this biphasic effect of estrogen eventually would be exploited therapeutically in situations in which attenuating growth was thought to be desirable. Tall adolescent girls wishing to minimize any further gain in height represented one such population. The first use of high-dose estrogen in girls with constitutional tall stature was reported by Goldzieher in 1956.[11] In the ensuing years, this practice became an established, if somewhat controversial, strategy for attenuating growth in these girls, and many reports have appeared in the literature.[12-15] The practice continues to this day, although less commonly, no doubt because of a decreasing sense of stigma associated with tall stature in

women.[16] Most of what is known about the effectiveness and potential adverse effects of high-dose estrogen treatment comes from these reports in this population.

The estrogen compounds used for growth attenuation, and the dosages used, have evolved across time and varied by region. In western and northern Europe, injectable estrogen compounds initially were used before being replaced by oral stilbestrol and eventually oral ethinyl estradiol (the estrogen most commonly used in oral contraceptives today). In the United States, the conjugated estrogen Premarin (Wyeth Pharmaceuticals Inc, Philadelphia, Pa; a combination of different estrogenic compounds derived from the urine of pregnant horses) was used predominantly.[12,13] Initially, doses greater than 10 to 15 times physiologic (or what was thought to be so at the time) were used, but eventually more modest doses were found to be as effective.[15] In most cases, severe uterine breakthrough bleeding occurred in girls taking estrogen alone, and a progestin was added at the end of the monthly cycle to induce normal menstrual periods.[12]

Although all reports claimed varying degrees of success in reducing adult stature, the amount of success varied. Most reported decreases in adult height were between 2 and 10 cm.[12-14] In most cases, treatment was not initiated until the girls were in early adolescence, and many had already had their first menses (a point at which girls will, on average, have already achieved 93% of their final adult height). Not surprisingly, the greatest reductions in height were seen when treatment was started earliest.[12]

How much reduction in height could we expect to achieve in young children using high-dose estrogen? Without prior experience, we can only reasonably speculate, and it would obviously depend on the child's age at the start of treatment. The younger the child at the beginning of treatment, the greater the reduction in height. We believe it a reasonable prediction, for example, 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). Older, larger children will see less of an effect.

THE RISKS OF TREATMENT

Because we have no direct experience with high-dose estrogen treatment in young children, the possible adverse effects and risks are difficult to assess with certainty. In adolescent girls treated for constitutional tall stature, reported adverse effects included nausea, headache, and weight gain, but these were generally mild and virtually never a reason for discontinuing treatment. Hyperprolactinemia has been reported but is generally of no clinical significance and resolves after treatment.[17] There is one report of a girl with a prolactinoma after high-dose estrogen treatment, but it is unclear whether this was a preexisting condition.[18] Recently, concerns about long-term effects on fertility in treated girls have been raised,[19] but clearly this is not relevant to our population.

The consequence of introducing high-dose estrogen in young prepubertal children will be significant. In boys, the only likely outward manifestation of estrogen exposure would be the development of gynecomastia. In girls, there will be rapid advancement of isosexual secondary sexual characteristics—most notably breast development and uterine bleeding. Uterine bleeding might be controlled by a combination of concurrent estrogen/progesterone treatment, but breakthrough bleeding is likely.[20] Although monthly or quarterly injections of depot medroxyprogesterone acetate are often used to control menses in some patients with severe developmental disabilities,[21,22] an alternative for these children is pretreatment hysterectomy, as was performed in our patient.

A word here about hysterectomy is probably appropriate. Hysterectomy in children, particularly in the disabled, is controversial and invariably associated with the negative connotations and history of forced "sterilization." But in these profoundly impaired children, with no realistic reproductive aspirations, prophylactic hysterectomy has several advantages as an adjunct to high-dose estrogen treatment. This onetime procedure eliminates the complications of menses, and in many cases, will spare the individual and her caregivers the expense, pain, and inconvenience of a lifetime of hormone injections. Hysterectomy also eliminates the need to give concurrent progesterone during the treatment phase, potentially reducing the risks of thrombosis.[23,24] It also eliminates the possibility of future uterine and cervical cancer. With the ovaries left in situ, hormones continue to be produced, providing some protection from osteoporosis. The risks of this surgical procedure in prepubertal girls, and the risks of long-term complications, are minimal— certainly they do not exceed the risk of similar procedures many of these children will experience as part of their medical care. The decision to perform hysterectomy should be made carefully, and the ethical (and legal) considerations important in making this decision have been discussed elsewhere.[25]

The most significant safety concern regarding high-dose estrogen treatment is the risk of thrombosis, most commonly deep vein thrombosis. The increased risk for developing deep vein thrombosis among women taking oral contraceptives is somewhere between 2- and 5-fold, increasing with age, although it is still relatively uncommon.[26,27] The risk of thrombosis also is increased among postmenopausal women receiving hormone therapy.[28] The mechanism through which estrogen increases thrombogenesis is not completely clear but probably is related to its direct effects on thrombotic factors.[29-32] Although concerns about the risk of thrombosis have been raised in the treatment of adolescent girls of tall stature,[33] few actual events have been reported. In combined reports of more than 700 girls with tall stature treated at 2 different centers, there was only 1 report of a mild deep vein thrombosis in a girl with a strong family history.[14,15] Weimann and Brack[34] also reported a case of deep vein thrombosis in a girl who had undergone arthroscopy during her treatment.

The actual risk of thrombosis in developmentally delayed children is difficult to assess. On the one hand, the risk of thrombosis seems decreased in the young; on the other, the risk is greater in those who are nonambulatory. Some evidence suggests that spasticity, a not uncommon finding in this population, might provide a measure of protection against thrombosis.[35] The risk might also be reduced by using transdermal estrogen, which we elected to do in our patient, and by performing pretreat-

ment hysterectomy, thus eliminating the need for progesterone. The risk in boys taking estrogen is probably similar to the risk in girls.[36]

THE ETHICAL DEBATE

There is not much doubt that growth can be attenuated significantly by using high-dose estrogen, particularly if undertaken in patients at an early age. But should it be? Is such an intervention in the best interest of these children?

There are good historical reasons to proceed cautiously when considering any intervention directed at persons with developmental disabilities. Past abuses against this population are well documented. During the late 19th and early 20th centuries, for example, many persons who had mental retardation (or who were thought to have mental retardation) were subject to involuntary sterilization because of the belief that they were genetically "unfit" and would pass their "defects" on to future generations.[37,38] In many cases, these individuals were capable of living independently, marrying, and raising children. These decisions were based not on the best interest of the patient but rather on the perceived interest of society and, in some cases, the interests of parents or caretakers.

The lessons of these and other abuses must be remembered, but past abuses should not dissuade us from exploring novel therapies that offer the potential for benefit. The population we propose to treat—children like our patient with profound cognitive and neurologic impairment, who are nonambulatory and wholly dependent on others for every need—is different from the mildly to moderately impaired. Nevertheless, we recognize the concern about inappropriate application of these procedures in children who are less severely disabled. To guard against the arbitrary application of growth-limiting therapy, it seems appropriate, even perhaps necessary, that a formal mechanism exists to ensure proper application of treatment. At our institution, we are convening an interdisciplinary group consisting of pediatric specialists in endocrinology, neurology, development, surgery, and ethics to consider each case on its merits. This same group will also carefully consider whether any additional procedures, such as hysterectomy, are appropriate and serve the interests of the child. Ideally, this approach might be combined with a research protocol approved by an institutional review board. Growth attenuation should be considered only after careful consideration of the risks and benefits to each patient on an individual basis.

When deciding whether it is ethically appropriate to attenuate growth in these children, there are 2 primary considerations. First, does growth attenuation offer the patient benefit? And second, does growth attenuation do any harm to the patient? The question here, then, is whether there is a reasonable expectation of improved quality of life for a nonambulatory child with profound developmental disability, and at what risk?

The primary benefit offered by growth attenuation is the potential to make caring for the child less burdensome and therefore more accessible. A smaller person is not as difficult to move and transfer from place to place. Although this may seem to be an advantage that accrues to the caretakers rather than the child, it offers several distinct benefits to the child as well. A child who is easier to move will in all likelihood be moved more frequently. Being easier to move means more stimulation, fewer medical complications, and more social interaction. Physical contact between parent and child is likely to be more direct and personal without the need for hoisting apparatus or other devices. Being easier to move and transfer also makes it more likely that the child will be included in family activities and family outings.

Finally, as we have already argued, parents often wish to continue caring for an older child but find themselves unable to manage the physical demands as their child grows to adult size. Although size may not be the only consideration, and not all parents will choose this option, growth attenuation may offer some parents at least the opportunity to extend the time they can care for their child at home, whereas otherwise institutionalization, or foster care, might be the only alternative.

For all of these reasons, growth attenuation in the nonambulatory child with severe developmental disability seems mutually beneficial to caretakers and patient. There does not appear to be a conflict between the interests of the parents and the interests of the child.

Having established a probable benefit to small stature, the second consideration derives from the ethical principle of nonmaleficence, *primum non nocere*, to "do no harm." Could growth attenuation cause harm to these children?

Several potential harms should be considered. Already mentioned are the possible medical adverse effects of high-dose estrogen, the most significant of which is the risk of thrombosis. Although these are real risks, they do not appear to be excessive and probably do not significantly exceed the risks of similar therapies used in this population to control menstruation or prevent pregnancy.

Can one imagine harm to this population from simply being small? Height and normal stature clearly have social value for most individuals. Being taller has been associated with enhanced social stature, greater pay, greater success in attracting a mate, and other social benefits.[39] However, a nonambulatory, severely impaired child is not someone who will experience these benefits of tall stature and therefore will not suffer their loss if kept short. For an individual who will never be capable of holding a job, establishing a romantic relationship, or interacting as an adult, it is hard to imagine how being smaller would be socially disadvantageous.

One might argue that being smaller might alter the way others interact with an older disabled person, perhaps tending to treat that person as a child instead of an adult. Whereas this might be an important issue for a short-statured adult who is capable of normal adult interactions, it is unlikely that such "infantilization" harms a person whose mental capacity will always remain that of a young child. In fact, for a person with a developmental age of an infant, smaller stature may actually constitute an advantage because others probably would be more likely to interact in ways that are more appropriate to that person's developmental age.

In summary, the harms associated with growth attenuation for persons with severe developmental disability are primarily those associated with the medical risks of treatment. These risks do not appear to be unreason-

able and are not out of line with the risks of other medical interventions these children undergo.

CONCLUSIONS

A parent's desire to seek growth attenuation for a permanently nonambulatory child with profound developmental, neurologic, and cognitive impairment would seem reasonable and understandable. We have argued that a compelling case can be made that the child will benefit from such treatment, that the risks of harm are limited to the adverse effects of the therapy, and that such risks do not significantly exceed those of other standard medical interventions.

To prevent the possibility of abuse and to ensure the safe administration and follow-up of therapy, we suggest that treatment should proceed only after evaluation by a pediatric neurodevelopmental specialist and with the supervision of a pediatric endocrinologist, preferably after review by the institution's ethics committee or in the context of a study reviewed by an institutional review board. Parents should be made aware of the risks and uncertainties of a novel, untested medical intervention. In the presence of those safeguards, we suggest that such treatment is both ethical and feasible and should be an option available to parents.

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