Mini Review

HORMONE RESEARCH IN PÆDIATRICS

Horm Res Paediatr 2017;87:145–152
DOI: 10.1159/000458526

Received: December 19, 2016
Accepted after revision: January 31, 2017
Published online: March 2, 2017

Growth Promotion Ethics and the Challenge to Resist Cosmetic Endocrinology

David B. Allen

University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Keywords
Human growth hormone · Ethics · Growth promotion · Enhancement · Cosmetic endocrinology

Abstract
The advancement of "human growth hormone (hGH)-for-height" – increasing height attainment in children short for reasons other than GH deficiency – arose from intuitive, deep-seated assumptions about the disability of short stature, its improvement with hGH-mediated height gain, and the safety of escalating dosages of hGH in healthy children. Evidence challenging these assumptions now strengthens criticism of hGH-for-height as cosmetic endocrinology. To counter this characterization, collective acceptance of guidelines is needed that advise nontreatment of the vast majority of short children, support strategies that minimize treatment duration and dosage, and restrain enhancement of normal adult stature. Through a clinical case analysis, ethical issues underlying these recommendations are explored. These include duties to provide informed assent and re-assent, protect children from unnecessary treatment, consider fairness to nontreated children, and allocate healthcare resources responsibly. Informed assent for hGH-for-height should ensure awareness of modest, variable height gain expectations, limited evidence for psychosocial benefit, ongoing studies for potential posttreatment adverse effects, and options for less expensive/invasive approaches, including nontreatment and counseling. Approaching growth promotion in this way fosters therapeutic restraint, resists the allure of enhancement therapy, and minimizes contributions to society's perception that to be taller is to be better.

Introduction

The advent of recombinant human growth hormone (hGH) marked a paradigm shift in pediatric endocrinology, expanding its scope beyond the replacement of deficient hormones and the suppression of excess hormones to include pharmacological hormonal augmentation therapy. A remarkable era of hGH therapeutic expansion ensued, spearheaded by industry and facilitated by pediatric endocrinologists [1]. The embracement of "hGH for height" (i.e., increasing height gain and attainment in children who are short for reasons other than GH deficiency [GHD]) arose from intuitive and deep-seated as-

KARGER

E-Mail karger@karger.com
www.karger.com/hrp

David B. Allen MD
H4/448 CSC Pediatrics
600 Highland Avenue
Madison, WI 53792-4108 (USA)
E-Mail dballen@pediatrics.wisc.edu

sumptions: (1) severe short stature in children is a disabling condition requiring and deserving of treatment; (2) hGH is safe for short children without GHD, even at escalating and supraphysiologic dosages; and (3) hGH-induced height improvement would measurably enhance quality of life. Today, however, the validity and value of each of these assumptions has been challenged, weakening conditions that favor hGH therapeutic expansion over restraint and giving credence to criticisms of cosmetic endocrinology [2]. As a result, justification of hGH-for-height as necessary and in the best interest of the treated child requires a higher threshold for honest appraisal of potential benefits and burdens and, at the same time, establishment of and adherence to therapeutic goals that are fair to all children.

Two points of clarification are needed. This discussion is about hGH treatment aimed at increasing stature and not about restoring hormonal normalcy in children with severe and permanent GHD, usually associated with hypoglycemia, identifiable central nervous system malformations, or multiple pituitary hormone deficiencies. There is agreement that children with severe GHD need to be treated, many into adulthood. Herein, isolated GHD (IGHD) refers to short, otherwise healthy children who have low stimulated GH levels but normal MRI scans, no other pituitary hormone deficiencies, and no other reason for GHD. Idiopathic short stature (ISS) refers to short, otherwise healthy children distinguished from IGHD only by higher GH testing results [3]. These two groups comprise the majority of and most controversial hGH-treated patients. That being said, justification for therapeutic objectives and benefit/burden assessments are also relevant for children with other conditions receiving hGH-for-height, including chronic renal insufficiency [4], Turner syndrome [5], born small for gestational age [6], SHOX deficiency [7], and Noonan syndrome [8]. (Prader-Willi syndrome is separated from this discussion by its more variable GH secretion and body composition rationale for treatment [9].) In addition, while hGH-for-height treatment is an appropriate subject of intense scrutiny given its widespread usage, cost, and theoretical potential for long-term risk, issues discussed below should be similarly considered for other height-increasing interventions.

Second, hGH-for-height is not considered here to be categorically worthwhile/justifiable or not. Variables influencing each child's situation and potential benefit from height change preclude such categorization. Guidelines and consensus statements on the treatment of short stature not related to GHD are available [10, 11] and, because good ethics always begin with good facts, readers are encouraged to review their assessments of FDA guidelines, interpretation of GH stimulation tests and IGF-I levels, hGH dosage, risks [12, 13], height-increasing benefits, and aspects of treatment follow-up. These guidelines do not, however, address how evidence regarding hoped-for quality-of-life improvement and other factors apart from the surrogate marker of height gain should influence when and whether to initiate, interrupt, and discontinue hGH-for-height treatment. Below, a true prismatic clinical vignette of twin boys – one treated with hGH – illustrates how consideration of relevant ethics issues prior to potential hGH initiation and subsequently at key clinical decision points can help clinicians and families choose hGH-for-height only when and for as long as necessary and to resist the allure of hGH enhancement [1] (Fig. 1).

Decision Point A: Initiating hGH-for-Height Treatment – A Proper, Necessary Medical Intervention?

Approval of hGH for non-GHD indications validated the notion that if hGH treatment is effective at increasing height in non-GHD children, then the etiology of short stature is not morally relevant in deciding who is entitled to treatment, i.e., such children all share a central, seemingly valid concern: "I am short and need to be taller" [14]. The difficulty is that the phrase "need to be taller" ranges in meaning for the child from "physically need to be taller" to "would feel better if I were taller" or "would make my parents feel better if I were taller," and for parents from "my child will be physically disabled by short stature as an adult" to "short stature will be a disadvantage in my child's social life and career" to "my child would feel better at a more normal height" [15]. However, in a world where talents and appearances are not and ought not to be distributed equally, some assert that acquiescing to patient wants rather than needs for hGH departs from medicine's proper role of helping people to be *normal* competitors, not *equal* competitors [16]. Distinguishing patient needs from desires is also one factor separating *treatment* from *enhancement* and thereby defining boundaries for medically necessary interventions. Administration of hGH is treatment, and therefore is deserved when it corrects disease and disability – defined as significant departures from normal function – and is not deserved when it merely lessens "unlucky" competitive disadvantage by enhancing performance or appearance [16].

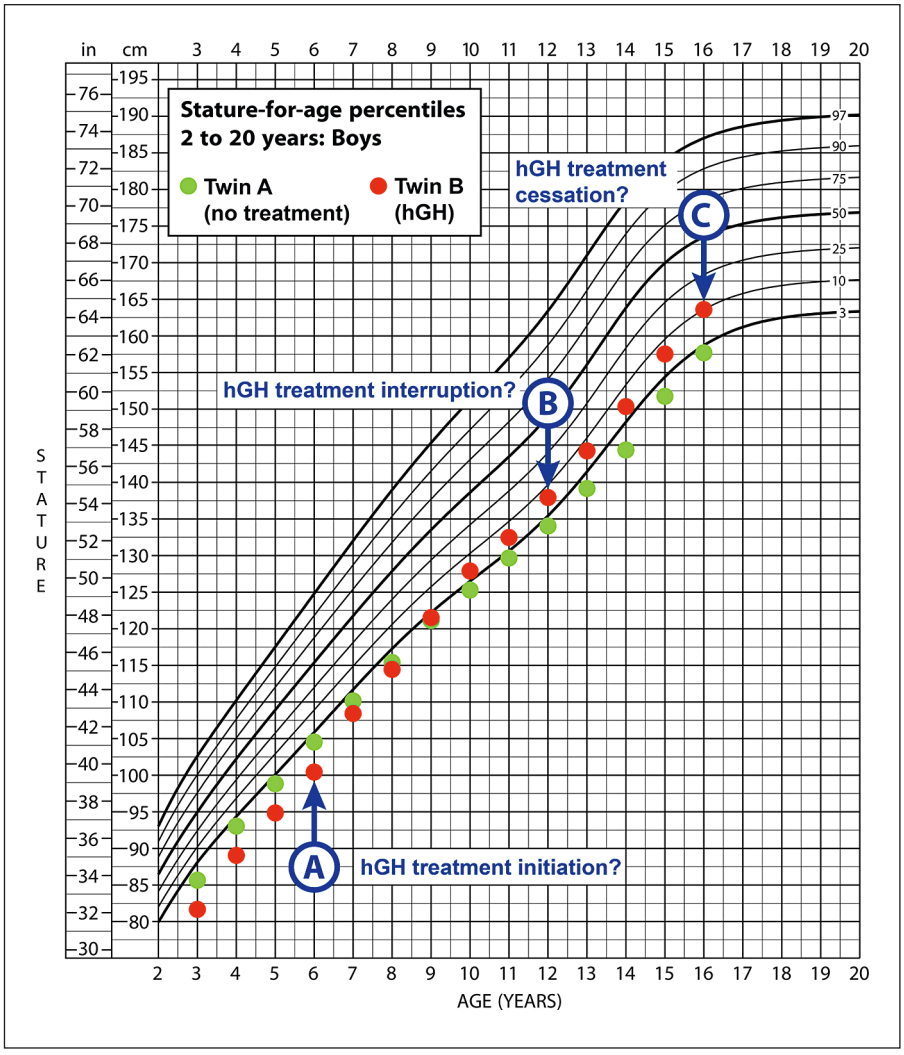

Fig. 1. Twin boys with persistent size discrepancy since birth present with short stature at the age of 3 years. Screening laboratory evaluation of the smaller twin is nonrevealing, and observation recommended. During kindergarten, concern about severe short stature and emotional well-being of the smaller twin prompts provocative testing (peak GH 8.5 ng/mL), MRI (normal), and (time A) institution of hGH. At time B, the hGH-treated twin is now taller than the untreated twin, prompting parental concerns of distress in the now shorter twin, and both are beginning puberty. At time C, the hGH-treated twin has reached a height in the lower-normal adult male range. Key questions for repeated informed assent discussions are posed for A–C.

Extension of growth-enhancing effects of hGH beyond children with GHD also challenged the relevance of traditional definitions of "disease" in determining entitlement to hGH treatment. Critics of hGH-for-height argued that the non-GHD child does not have a disease and that use of hGH in such a situation constitutes enhancement, implicitly an inappropriate goal of the practice of medicine. However, to the child and parent, it is irrelevant whether the condition being treated is a well-characterized "disease" caused by GHD or a less well-understood process, as is the case in Turner syndrome and ISS. The object of concern is not GHD, but short stature, and the only relevant question is whether there is safe, effective, affordable treatment. During the past several years, an additional emerging counterpoint to the enhancement criticism is that severe short stature is a maladaptive condition rooted in biology, whether in genes or an abnormal pituitary gland, and that these biological underpinnings of short stature represent physiological *defects* rather than variations or alterations [17]. This notion endorses therapeutic expansion of hGH-for-height by implying that costly treatment to overcome such defects is a medically necessary endeavor.

Even more central to the decision to initiate hGH treatment is whether short stature confers a current and/or future disability that warrants medical intervention. In a minority of cases, when severe short stature is or will be physically debilitating (e.g., requiring special accommodations for driving or reaching shelves), offering effective growth promotion treatment can align with medical necessity. More commonly, motivation for seeking treatment invokes the narrative that distress in short children

is due to their shortness, an assumption forged from early studies of children with mostly severe GHD referred to specialists and our own experiences with worried parents and anxious children. In fact, while people tend to attribute significantly less favorable characteristics to short people, research predominantly and repeatedly fails to detect an excess of psychosocial adaptation problems among short-statured youths themselves [18]. Although short stature is associated with teasing and a tendency to treat the child as if younger than their chronological age [19], both in-clinic [20] and population-based [21] studies indicate that these stressors are not typically associated with impaired function. Persistent tendency to presume that short stature is predictably and causally related to negative outcomes suggests a "focusing illusion" in which judgments about a characteristic derived from a subset are applied globally to all subjects with the characteristic [18]. Accordingly, even though these and other similar studies [22] do not exemplify all severely short children coming to our clinics, we must accept that psychological morbidity, while possible, is not a predictable consequence of short stature. This does not mean, however, that no short children should be treated with hGH. Although difficult to define, some degree of disordered growth, like disfiguring physical traits, ought to be considered appropriately within the realm of medicine and initiation of hGH-for-height aligned with medicine's proper role to help people to be normal competitors.

A pediatric care provider's duty to the child involves both providing necessary treatment while also protecting him/her from unnecessary or ineffective interventions. When treatments are not crucial for maintenance or restoration of health, this responsibility becomes paramount, and parental autonomy more complicated. Plausible concerns regarding post-hGH treatment adverse effects [23, 24] have led to calls for further research of its life-long safety [25, 26] and disclosure to patients and families that such investigations are needed and underway [27]. Further, because safety is a relative concept affected by illness severity and availability of alternative effective options (including no treatment), for short, otherwise healthy children, even a small risk for a long-term adverse effect may not be outweighed by an unpredictable and poorly defined benefit [15].

Thus, for hGH-for-height that does not improve physical health, and for which improved psychosocial well-being is the primary therapeutic objective, we are challenged to convey uncertainty about the benefit/burden analysis during pretreatment discussions with parents and children. Ethical and evidence-based counseling for parents at decision point A would therefore include the following: while concern about your child's short stature is understandable, (1) your child's height is most likely not the primary factor affecting his/her psychological well-being [18]; (2) hGH treatment will improve the growth rate and may modestly increase height attainment, but has not been shown to predictably improve psychosocial well-being [28]; and (3) it is therefore uncertain to what degree the benefits of treatment outweigh the risks, however small, for your otherwise healthy child [29]. For children who are old enough to provide informed assent (e.g., 10–12 years of age, see below) at decision point A, inclusion in the hGH initiation assenting process is appropriate, and given the discretionary nature of the intervention, serious consideration should be given to nontreatment if the child dissents.

Decision Point B: hGH-for-Height Interruption – A Responsibility to Reassess the Need for and Assent to Continued Treatment?

To the hGH-treated child in front of us, it is understandable to feel a duty to provide the best possible height outcome. Thus, it is not surprising that standard practice is generally for hGH-for-height to continue uninterrupted until epiphyseal closure or a height subjectively considered satisfactory by the child, family, and physician is attained. The presumed benefit of hGH-for-height, however, is relative to the height of others, so that social and economic advantages accrue to the hGH-treated person at the expense of another nontreated and now relatively shorter person. As vividly illustrated by the clinical vignette, the hGH-treated child's interest in and entitlement to greater height does not necessarily correlate with either his brother's or society's interest; i.e., the height disparity becoming apparent within this family is also occurring with other children on the playground. Although it is untenable to titrate hGH treatment to avoid passing nontreated children, it is possible to take steps to better balance the duty to the hGH-treated child with fairness to all children.

One such opportunity arises at pubertal onset (decision point B). In the absence of unequivocal GHD, continuing treatment uninterrupted until maximum height assumes the child needs hGH to that point (a medical question) and is entitled to it (an ethical question). A majority of children diagnosed with IGHD show normal GH secretion and sustained normal growth to normal height after the onset of puberty [30], and withdrawal of hGH

treatment at onset of puberty in such patients does not adversely affect height attainment [31]. Consequently, for pubertal children with IGHD or ISS whose height prognosis now falls within the low-normal adult range, routine cessation of hGH followed by re-testing of GH secretion if persistent IGHD is still suspected and a period of growth rate observation of non-GHD patients is reasonable. While controlled studies of hGH cessation at the onset of puberty in ISS children are (disappointingly but not surprisingly) lacking, normal endogenous sex hormone and GH production will cause most to continue to grow well, potentially saving years of expensive treatment. More germane to this discussion, this approach protects such children from unnecessary treatment and minimizes deliberately making some now-normal-statured children taller than others. It also contrasts sharply with pubertal dose escalation advanced by industry-sponsored trials [32] and emblematic of the "maximum attainable height" narrative.

Decision point B also connotes a time of responsibility to more deeply involve the emerging adolescent in formal assent to ongoing hGH treatment. Balancing risks and benefits of dose escalation and treatment prolongation become particularly complex when pediatric patients have the maturity to participate in decision-making but are not yet empowered to make their own healthcare choices. Whereas decisions regarding earlier life initiation of hGH-for-height heavily reflect parental concerns and physician attitudes [33], these may or may not still align with the hGH-treated adolescent's views. In addition, pre-eminence of parental autonomy is less clear when treatments are not essential for health and yet have potential risks that are borne by the child. Accordingly, professional organizations and the courts support the inclusion of older children in formally assenting to healthcare decision-making, usually around the age of 12 years [27]. Therefore, emerging hGH-for-height-treated adolescents should be informed about the likelihood of continued height gain without hGH, theoretical safety concerns prompting ongoing posttreatment studies, and the reasonableness of foregoing daily injections during a period of treatment interruption and observation.

Decision Point C: Therapeutic Objective – A Duty to Deliver Maximal Height or Normal Height?

The mainstream hGH-for-height narrative equates maximum height gain with expected and commensurate improvements in quality of life that justify its cost and potential risk. An alternative narrative asks whether hGH-for-height makes children better off, not just taller, and if so, to what height is treatment justified? Again, it has been difficult to validate prior assumptions. In young adults with ISS or who were small for gestational age, neither hGH treatment nor untreated short stature correlated with long-term positive or negative psychosocial effects, respectively [34]. Even among previously hGH-treated young women with Turner syndrome, height was not related to psychosocial parameters [35]. In general, psychosocial studies following hGH treatment are still few in number, limited by small sample size, and usually at high risk of bias in their design or execution [36]. The available evidence suggests that hGH does not predictably improve psychosocial well-being for most children, even when such treatment increases the surrogate measure of final height – information that should be included, as mentioned above, in the informed assent process before initiating hGH-for-height. In fact, with regard to longevity, a growing body of evidence suggests that, within generally healthy environments, shorter people may actually live longer [37].

With this is mind, should the aim of hGH-for-height be an adult height within the lower statistically normal range, a height matching other members of the family, or the tallest height that is attainable? Determining a responsible endpoint for hGH-for-height challenges us to distinguish between what patients want and what they truly need. Regardless of diagnosis, continuing treatment until the child reaches maximum height substantially increases costs [29], with the last 1–3% of potential height gain increasing total expenditure by ~20% [38]. Thus, for the adolescent treated for short stature due to any cause who has achieved a height in the low-normal adult range, the mere fact that he or she can claim potential to be taller with continued treatment does not justify entitlement to highly expensive therapy. Further, without evidence that increased height proportionately improves patient well-being, treatment endpoints also cannot be differentiated according to quality-of-life outcomes [29]. It is difficult to defend that children with any short-stature-associated diagnosis are entitled to subsidized hGH-for-height (or any other growth-promoting) treatment beyond a height within the statistically normal adult range.

Although it might be particularly disappointing for tall parents to have a relatively short child, parental expectations or desires cannot be the basis for entitlement to GH therapy. Putting parental disappointment aside and adhering to a statistical "normal opportunity range" therapeutic goal coincides with healthcare-with-justice aims to

provide opportunities to achieve generally accepted benefits of life in our society. There is no coherent claim that anyone is entitled to communal resources to maximize his/her opportunities, whether in food, shelter, education, healthcare, or income [16]. Families could justifiably choose to use personal resources to pursue additional treatment to maximize height attainment within the normal adult range. Society generally tolerates individual discretion in spending earned income for health matters, particularly if these decisions do not cause harm to those who could not afford treatment. Given the apparently modest gains produced by hGH-for-height treatment in most non-GHD children, it is unlikely that there would be severe overall harm. The inequality likely to be produced by such private purchases may indeed be trivial as compared with other consequences of inequality of wealth.

In summary, decision points A, B, and C provide opportunities to combine ethical considerations with evidence in directing hGH-for-height treatment to extremely short children truly impaired by stature, using it judiciously and cost-effectively in those that are, and not asking for public/insurance support for discretionary treatment of normal-adult-statured patients, regardless of etiology.

The Big Picture: Cosmetic Endocrinology – Do We Have a Defense?

The story of hGH-for-height is a vivid example of expansive biotechnology [39], in which medical interventions that begin as treatments for disease or severely disabling conditions expand into therapies that reduce disability, lessen disadvantage, or even confer advantage. In the expansive biotechnology environment, forces that propel profitable drugs, devices, and procedures often dominate over considerations of efficient and equitable distribution of resources. This dominance is augmented by shared vested interests of parents, well-intending prescribers, and industry and often biased by prior assumptions, reliant on surrogate outcomes, and advantageous to marketing. Interventions are justified by "medicalization" of physiologic variations like short stature as defects or disease, and nudged into standard practice by key opinion leaders. As a result, it is challenging to discern when or whether benefits of hGH-for-height offered and aimed for clearly belong in the healthcare system.

Pediatric endocrinology became entangled with the expansion of hGH therapy through collaboration with industry-sponsored research and safety surveillance studies which explored higher dosages and new indications for hGH [25]. This resource-abundant environment, however, was too good to be all good. Most studies were noncontrolled, observational, and focused primarily on increased short-term growth rate and predicted height. At the same time, clinic volumes and relative value units increased, and for many of us, leadership positions, lecture invitations, and publications advanced academic careers. Thus, expansion of hGH-for-height treatment was nurtured not only by opportunities to help patients, but also by benefits for our careers and specialty [1].

For 30 years, the allure of alleviating presumed consequences of short stature carried pediatric endocrinology beyond physiological hGH replacement to pharmacological hGH-for-height enhancement. Today, restrictions on healthcare funding are combining with uncertainties about true benefits of hGH-for-height and its conceivable long-term risks to undermine the height promotion enterprise. Third-party support is dwindling and categorical exclusions of hGH therapy outside of replacement of unequivocal GHD increasing. Further, as long as hGH remains costly, the moral question about fair allocation of resources in environments that do not provide basic healthcare for all merits attention. Moreover, if and when hGH becomes affordable, responsible prescribing of hGH will still be problematic, since hGH augmentation may not be so free of potential long-term effects to recommend its elective use in healthy children without a defined benefit. In 1985 (when the author began fellowship training), the atmosphere was one of helplessness and foreboding as families of pituitary GH-treated children were notified of the risk for Jakob-Creutzfeldt disease. But for almost all of these children who had profound GHD, at least pituitary GH *had to* be prescribed. However unlikely, it is still worthwhile to ponder an unanticipated long-term serious adverse effect in today's children for whom hGH treatment is discretionary.

The era of height enhancement as a primary driving force sustaining research, education, and growth in physician number in pediatric endocrinology is coming to an end. Voices aiming to restrain hGH-for-height treatment have become emboldened: "The story of treating stature is ultimately the story of temptation; the temptation of parents trying everything to secure their child's current and future happiness and success; the temptation for doctors who want to help children grow and believe that they can alleviate suffering, even of the social variety, with a prescription; the temptations of industry to provide a medical fix for social problems" [40]. However, lack of

evidence for predictable benefit from hGH-for-height treatment in most children does not mean that no short children should be treated. In children with Turner syndrome, renal failure, and other growth-compromising disorders, the stress of dealing with other comorbidities could amplify an adverse psychological effect of short stature. Even in otherwise healthy children, although difficult to define, some degree of disordered growth could be, like disfiguring physical traits, considered disabling and its treatment appropriately within the realm of medicine.

Helping children who cannot grow normally to do so will always be a central and immensely satisfying part of pediatric endocrinology – so the end of the hGH era will not, and should not, be the end of hGH-for-height therapy. However, to counter criticisms of "cosmetic endocrinology" with some ethical clarity, future guidelines for responsible growth promotion treatment could assist by (1) recommending nontreatment to the vast majority of short children that do not have a problem solved by growth promotion and restricting treatment to severe and (likely) disabling short stature, (2) promoting strategies that minimize hGH treatment duration and dosage, and incorporate less expensive and less invasive alternative approaches (e.g., counseling, oxandrolone [29], possibly aromatase inhibitors [41]), and (3) strongly discouraging the enhancement of normal adult stature by any means. Finally, informative and honest counseling of potential hGH-for-height recipients should include discussion of realistic, modest, and variable height gain, limited evidence for psychosocial benefit, and ongoing studies for potential post-treatment adverse effects. Such an approach would demonstrate that our specialty is willing and capable of exercising thoughtful restraint in growth-promoting therapy in general, and of minimizing any contribution to society's perception that to be taller is to be better.

Acknowledgements

The author wishes to thank colleagues Ellen Connor, Allison Pollock, and Brittany Allen for their insightful reviews of the manuscript.

Disclosure Statement

Dr. Allen has no conflicts of interest to report relevant to the preparation or content of the manuscript.

References

1 Allen DB: Clinical review: lessons learned from the hGH era. J Clin Endocrinol Metab 2011;96:3042–3047.

2 Rosenbloom AL: Pediatric endo-cosmetology and the evolution of growth diagnosis and treatment. J Pediatr 2011;158:187–193.

3 Wit JM, Reiter EO, Ross JL, Saenger PH, Savage MO, Rogol AD, Cohen P: Idiopathic short stature: management and growth hormone treatment. Growth Horm IGF Res 2008;18:111–135.

4 Vimalachandra D, Craig JC, Cowell CT, Knight JF: Growth hormone treatment in children with chronic renal failure: a meta-analysis of randomized controlled trials. J Pediatr 2001;139:560–567.

5 Baxter L, Bryant J, Cave CB, Milne R: Recombinant growth hormone for children and adolescents with Turner syndrome. Cochrane Database Syst Rev 2007:CD003887.

6 de Zegher F, Ong KK, Ibanez L, Dunger DB: Growth hormone therapy in short children born small for gestational age. Horm Res 2006;65(suppl 3):145–152.

7 Blum WF, Crowe BJ, Quigley CA, Jung H, Cao D, Ross JL, Braun L, Rappold G: Growth hormone is effective in treatment of short stature associated with short stature homeobox-containing gene deficiency: two-year results of a randomized, controlled, multicenter trial. J Clin Endocrinol Metab 2007;92:219–228.

8 Lee PA, Ross J, Germak JA, Gut R: Effect of 4 years of growth hormone therapy in children with Noonan syndrome in the American Norditropin Studies: Web-Enabled Research (ANSWER) Program® registry. Int J Pediatr Endocrinol 2012;2012:15.

9 Carrel AL, Myers SE, Whitman BY, Eickhoff J, Allen DB: Long-term growth hormone therapy changes the natural history of body composition and motor function in children with prader-willi syndrome. J Clin Endocrinol Metab 2010;95:1131–1136.

10 Grimberg A, DiVall SA, Polychronakos C, Allen DB, Cohen LE, Quintos JB, Rossi WC, Feudtner C, Murad MH: Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-I deficiency. Horm Res Paediatr 2016;86:361–397.

11 Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, Chernausek SD, Savage MO, Wit JM: Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. J Clin Endocrinol Metab 2008;93:4210–4217.

12 Allen DB, Backeljauw P, Bidlingmaier M, Biller BM, Boguszewski M, Burman P, Butler G, Chihara K, Christiansen J, Cianfarani S, et al: GH safety workshop position paper: a critical appraisal of recombinant human GH therapy in children and adults. Eur J Endocrinol 2016;174:P1–P9.

13 Sävendahl L, Maes M, Albertsson-Wikland K, Borgström B, Carel J-C, Henrard S, Speybroeck N, Thomas M, Zandwijken G, Hokken-Koelega A: Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGhE study. J Clin Endocrinol Metab 2012;97:E213–E217.

14 Allen DB, Fost NC: Growth hormone therapy for short stature: panacea or Pandora's box? J Pediatr 1990;117:16–21.

15 Allen DB: Growth hormone therapy for short stature: is the benefit worth the burden? Pediatrics 2006;118:343–348.
16 Daniels N: Normal functioning and the treatment-enhancement distinction. Camb Q Healthc Ethics 2000;9:309–322.
17 Savage MO, Burren CP, Rosenfeld RG: The continuum of growth hormone-IGF-I axis defects causing short stature: diagnostic and therapeutic challenges. Clin Endocrinol 2010;72:721–728.
18 Sandberg DE, Gardner M: Short stature: is it a psychosocial problem and does changing height matter? Pediatr Clin North Am 2015;62:963–982.
19 Meyer-Bahlburg HF: Short stature: psychological issues; in Lifshitz F (ed): Pediatric Endocrinology, ed 2. New York, Marcel Dekker, 1990, pp 173–196.
20 Sandberg DE, Brook AE, Campos SP: Short stature: a psychosocial burden requiring growth hormone therapy? Pediatrics 1994;94:832–840.
21 Sandberg DE, Bukowski WM, Fung CM, Noll RB: Height and social adjustment: are extremes a cause for concern and action? Pediatrics 2004;114:744–750.
22 Theunissen NC, Kamp GA, Koopman HM, Zwinderman KA, Vogels T, Wit JM: Quality of life and self-esteem in children treated for idiopathic short stature. J Pediatr 2002;140:507–515.
23 Carel J-C, Ecosse E, Landier F, Meguellati-Hakkas D, Kaguelidou F, Rey G, Coste J: Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. J Clin Endocrinol Metab 2012;97:416–425.
24 Poidvin A, Touze E, Ecosse E, Landier F, Bejot Y, Giroud M, Rothwell PM, Carel JC, Coste J: Growth hormone treatment for childhood short stature and risk of stroke in early adulthood. Neurology 2014;83:780–786.
25 Allen DB: Growth hormone post-marketing surveillance: safety, sales, and the unfinished task ahead. J Clin Endocrinol Metab 2010;95:52–55.
26 Rosenfeld RG, Cohen P, Robison LL, Bercu BB, Clayton P, Hoffman AR, Radovick S, Saenger P, Savage MO, Wit JM: Long-term surveillance of growth hormone therapy. J Clin Endocrinol Metab 2012;97:68–72.
27 Laventhal NT, Shuchman M, Sandberg DE: Warning about warnings: weighing risk and benefit when information is in a state of flux. Horm Res Paediatr 2013;79:4–8.
28 Ross JL, Sandberg DE, Rose SR, Leschek EW, Baron J, Chipman JJ, Cassorla FG, Quigley CA, Crowe BJ, Roberts K, et al: Psychological adaptation in children with idiopathic short stature treated with growth hormone or placebo. J Clin Endocrinol Metab 2004;89:4873–4878.
29 Allen DB, Cuttler L: Clinical practice. Short stature in childhood – challenges and choices. N Engl J Med 2013;368:1220–1228.
30 Tauber M, Moulin P, Pienkowski C, Jouret B, Rochiccioli P: Growth hormone (GH) retesting and auxological data in 131 GH-deficient patients after completion of treatment. J Clin Endocrinol Metab 1997;82:352–356.
31 Zucchini S, Pirazzoli P, Baronio F, Gennari M, Bal MO, Balsamo A, Gualandi S, Cicognani A: Effect on adult height of pubertal growth hormone retesting and withdrawal of therapy in patients with previously diagnosed growth hormone deficiency. J Clin Endocrinol Metab 2006;91:4271–4276.
32 Mauras N, Attie KM, Reiter EO, Saenger P, Baptista J: High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. Genentech, Inc., Cooperative Study Group. J Clin Endocrinol Metab 2000;85:3653–3660.
33 Silvers JB, Marinova D, Mercer MB, Connors A, Cuttler L: A national study of physician recommendations to initiate and discontinue growth hormone for short stature. Pediatrics 2010;126:468–476.
34 Visser-van Balen H, Geenen R, Kamp GA, Huisman J, Wit JM, Sinnema G: Long-term psychosocial consequences of hormone treatment for short stature. Acta Paediatr 2007;96:715–719.
35 Bannink EM, Raat H, Mulder PG, de Muinck Keizer-Schrama SM: Quality of life after growth hormone therapy and induced puberty in women with Turner syndrome. J Pediatr 2006;148:95–101.
36 Gardner M, Boshart ML, Yeguez CE, Desai KM, Sandberg DE: Coming up short: risks of bias in assessing psychological outcomes in growth hormone therapy for short stature. J Clin Endocrinol Metab 2016;101:23–30.
37 Samaras TT: We are too tall. Public Health Nutr 2009;12:439.
38 Finkelstein BS, Imperiale TF, Speroff T, Marrero U, Radcliffe DJ, Cuttler L: Effect of growth hormone therapy on height in children with idiopathic short stature: a meta-analysis. Arch Pediatr Adolesc Med 2002;156:230–240.
39 Buchanan A: Growth hormone: a paradigm of expansive biotechnologies. Endocrinologist 2001;11:78S–82S.
40 Cohen S, Cosgrove C: Normal at Any Cost: Tall Girls, Short Boys, and the Medical Industry's Quest to Manipulate Height. New York, Jeremy P. Tarcher/Penguin, 2009.
41 Mauras N, Ross JL, Gagliardi P, Yu YM, Hossain J, Permuy J, Damaso L, Merinbaum D, Singh RJ, Gaete X, et al: Randomized trial of aromatase inhibitors, growth hormone or combination in pubertal boys with idiopathic short stature. J Clin Endocrinol Metab 2016:jc20162891.