Feeling misguided: a comment on the US guidelines on growth hormone and insulin-like growth factor-I treatment in children and adolescents

Paul Saenger[a] *and Pinchas Cohen*[b]

The growth hormone (GH) treatment Guidelines by Grimberg *et al*. [1] on behalf of the Drug and Therapeutics Committee and Ethics Committee of the US Pediatric Endocrine Society (PES) were long overdue and comprehensive. Unfortunately, there are several aspects of this work that raise concern in the Pediatric Endocrine communities. First, it only puts forth North American views. In the age of globalization, input from sister societies (ESPE, SLEP, JPES and so on) would have timely and welcome as noted in a recent commentary by Ranke and Wit [2]. Second, it approaches the topic with the rigor typically used in fields such as hypertension and hypercholesterolemia, where dozens of very-large, long-term randomized trials are regularly being conducted; ignoring the fact that in pediatric short stature, randomized trials are infrequent, small and rarely conducted till adult height, and smaller studies must be considered. In fact, the relatively long interval that has elapsed since the previous PES 2003 guidelines is a result of the paucity of new research in the field. Third, these treatment guidelines blurred the lines between practice and ethics, and represent the views of a legitimate but not unanimous component of the US Pediatric Endocrine community. The group that crafted these guidelines was selected not for its expertise in the growth field but with an 'ideological' litmus test [3] whereby only individuals who did not report honoraria or grant support from GH manufacturers were allowed to participate, representing a departure from the commonly accepted practice of allowing experts to participate in such activities as long as they fully list their conflicts. Moreover, several members of the PES Drugs and Therapeutics Committee have indicated that they had no input into the document and had not necessarily agreed with all of its contents. Furthermore, while PES policy requires a period of public comment on a draft of such guidelines, scores of comments, including lengthy and thoughtful comments from the two authors of this commentary and multiple other highly regarded experts, were simply brushed off and ignored. During this public comment period preceding the publication of the Guidelines, two issues sparked the most interest and commentary. These two issues were: benefits of insulin like growth factor-1 (IGF-1)-based GH dosing and sex steroid priming in the evaluation of GH deficiency. These two issues will be addressed in this invited, brief commentary.

Regarding IGF-based dosing. Grimberg *et al*. stated that they cannot make a recommendation regarding IGF-I-based dosing because there are no published adult height data using this method as well as citing concerns about potential risks and cost. At the same time, they recommend 'measurement of serum IGF-I levels' as a tool to monitor adherence and IGF-I production in response to GH dose changes and suggest that the GH dose be lowered if serum IGF-I levels rise above the laboratory-defined normal range; however, they only give this advice 'conditional recommendation'. By doing so, they ignore the impact of multiple randomized studies demonstrating the value of IGF-based dosing, which has been designed precisely for the purpose of improving GH safety [4]. Furthermore, a detailed analysis of IGF-based dosing demonstrated that using this approach actually results in lower GH doses than conventional weight-based dosing and achieves far fewer elevated IGF-I measurements [5] as well as having lower overall costs. Refusal to accept these studies which involved a randomized 2-year protocol is curious in the context of the fact that the Food and Drug Administration (FDA) will

[a]NYU Winthrop University Hospital, Mineola, NY and [b]University of Southern California, Los Angeles, California, USA

Correspondence to Paul Saenger, Prof of Pediatrics, NYU Winthrop University Hospital, Mineola NY 11501, USA.
E-mail: phsaenger@gmail.com

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soon approve new growth-promoting drugs (in the form of multiple different long-acting GH products) based on 1-year studies, and randomized studies to final-height will never be performed [6]. However, the failure to recommend the practice of IGF-based dosing will have little practical effect on how US pediatric endocrinologists practice, as the vast majority of them use this approach regardless [7,8]. However, the apparent recommendation to require sex steroid priming for the diagnosis of GHD could actually have a serious negative impact on the field, limiting flexibility in physician practice within FDA guidelines and enabling payers in undermining patient reimbursement.

There is no evidence that priming with sex steroids (estrogen or testosterone) is physiologic in the peripubertal child. It is a pseudoscientific maneuver with rather vague dosing suggestions and a complete lack of standardization of methodology. Priming is akin to performing a glucose tolerance test (GTT) in teenager suspected of having type-2 diabetes mellitus after injecting the unsuspecting patient with a dose of subcutaneous insulin at the outset of the GTT – the results will be normal, yet camouflage a potential serious disease. A 9 to 11-year-old child's hypothalamic pituitary axis does not see pubertal estrogen or testosterone levels because they simply are not there. Thus, priming creates an artificial neuroendocrine environment with little connection to reality.

The history of the impact of gonadal steroid hormone action on GH secretion during childhood and adolescence was first reviewed by Kerrigan and Rogol in 1982 [8] and advanced our understanding of neuroendocrine interaction; but it is a leap of faith to make this observation an integral part of the instrumentation required for the correct diagnosis of GH deficiency. Witness the fact that past recommendations of the GRS and ESPE and LWPES in 2000 and most recently in 2008 [9–11] wisely do not recommend sex steroid priming in the evaluation of GH deficiency in peripubertal children. It is true that in a report by Marin *et al*. [12] which analyzed the effects of estrogen priming and puberty on GH responses in normal boys and girls, it was shown that the putative improved diagnostic efficiency was most significantly in individuals in Tanner stages –4 and –5, when there is endogenous hormone production. An important concern with sex steroid priming, however, is that it may lead to the under diagnosis of GH deficiency in peripubertal or early pubertal children. Priming may thus lead to a temporary but through a wholly artificial augmentation of GH secretion, followed by a return to possibly insufficient, spontaneous GH secretion, resulting in continued impaired linear growth [12]. Historically, sex steroid priming in peripubertal children was primarily used to identify complete GH deficiency and the extreme need for treatment with GH replacement at a time when there was scarce availability of GH [13]. With the advent of biosynthetic GH, this argument has become moot and we do not see a need for its reintroduction. A more targeted approach based on individual practice approaches may be reasonable.

If a physician wishes to use sex steroid priming, it is certainly his/her choice, just as the choice of the stimulation agent itself is center-specific and insulin or a host of other stimuli for GH testing might be performed back to back or on separate days. It is best to leave this to individual local preferences, but it should not be embedded into the official Guidelines of the PES without appropriate evidence so that it does not result in harm to patients who are artificially diagnosed as GH-sufficient. These Guidelines may become welcome fodder from third-party payers demanding that priming must be done in all short peripubertal children undergoing testing for GH sufficiency, very much like enforcing GH dosing restrictions gleaned from outdated package inserts dictating GH dosing in daily practice already now.

The clinical diagnosis of GH deficiency should be based on a combination of auxological data (growth failure and low growth velocity), biochemical data, (IGF-1 and IGF binding protein-3 in very young children), neuro radiological data, genetic data and unprimed GH stimulation testing [14]. The diagnosis of GH deficiency in children is difficult, but requiring sex steroid priming surely will not help and the decision of whether to use sex steroid priming should remain with the individual physician.

As noted above, there is no definitive evidence, for or against sex steroids priming. There is, however, logic and rationale in believing that children who need the sex steroids to promote their GH secretion and will spend years before their sex steroids levels are adequate, are functionally (albeit transiently) GH deficient.

If the purpose of this priming is simply to identify the fewest children who pass GH stimulation tests, there are many other things that one can require, from lowering the pass rate to 7 ng/ml (or 5, or 3), to require monoclonal GH assays, and to insist on insulin hypoglycemia as a stimulus. The most extreme case is to require that everyone will pass a growth hormone releasing hormone stimulation, even though it is obvious that kids with a hypothalamic abnormality will pass this test.

It is clear from registry databases and informal polling, that the majority of pediatric endocrinologists in the United States as well as in the rest of the

world do not sex-steroid prime. We believe that the role of PES should be much like that of the US Supreme Court deciding on issues such as gay marriage, healthcare or abortion. One can weigh arguments for and against, but in the end, if the decision goes against popular public opinion and the benefit of patients, it fails to serve the community that the society has been entrusted in supporting.

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