

## **Steroid Priming of GH Stimulation in the Peripubertal Age**

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Sex hormones administration prior to growth hormone (GH) stimulation testing is used to improve the accuracy of the diagnosis of GH deficiency.

The diagnosis of GH deficiency in childhood and adolescence has been a subject of much controversy (1-8). GH testing in peripubertal children is confounded by the lack of consensus on the use of priming with sex steroids before assessment of the GH-IGF-I axis (8-10). A survey among 235 members of ESPE conducted in 2001 showed that 50.2% of the respondents used sex steroid priming in boys and 40.9% in girls (9). Wyatt et al, in a survey of 251 pediatric endocrinologists in the United States, demonstrated that only one-third of them primed peripubertal children (10).

Teenage children with a constitutional delay in growth and puberty (CDGP) often exhibit very low GH secretion following stimulation while still prepubertal or in early puberty, but show a normal increase as puberty progresses (11-14). Considering that the rise in sex steroid concentrations, especially estrogens, in puberty leads to an increase in GH secretion (15-17), the abnormal GH responses in children with CDGP could be attributable, at least in part, to the lack of sex steroids at the time of initial testing. Thus, the administration of estrogen or testosterone for a few days before a GH provocative test may augment the GH response and make it possible for the clinician to distinguish between genuine GH deficiency and CDGP.

Marin et al. demonstrated the need for sex steroid administration in provocative GH testing in children of normal stature. When estrogen was not administered, serum GH concentrations failed to rise above 7ng/ml in 61% of the normal prepubertal children and 44% of the Tanner-stage-II children after 3 provocative tests: standardized treadmill exercise, arginine tolerance test, and insulin tolerance test. The administration of estrogen increased GH levels to above 7.2 ng/ml in 95% of these children (18). There are also several reports showing that sex-steroid priming in healthy peripubertal children with growth retardation eliminated more than half the patients initially diagnosed as having inadequate GH secretion on standard GH provocative tests (19-22). Moreover, administration of exogenous sex steroids increased the GH response to stimulation even in children with GH deficiency (23-24). Although sex steroids priming has been proposed to improve the GH response, there are no established criteria for the age of administration, the dose and the schedule for the sex hormones that are used in priming.

While the policy of most specialists is to prime boys aged >9 years and girls aged > 8 years, others tend to prime only children with delayed puberty at age >13 or 14 years in boys and >11 or 12 years in girls. This inconsistency was confirmed in the 2001 ESPE survey, which demonstrated that priming was used in boys from a mean age of  $10.6 \pm 0.18$  years, and in girls from a mean age of  $9.24 \pm 0.21$  years (9).

The lack of clear guidelines also extends to the hormone preparation, dose and schedule for use in priming. Different kinds of sex hormone preparations in various doses have been suggested (17-24). Generally, in boys, intramuscular testosterone depot 100-200 mg is injected 10 days before GH testing; in girls, oral estrogens, either ethinyl estradiol  $40\text{mcg/m}^2$  or conjugated estrogen 1.25 mg/day, are prescribed for 2 to 3 days before testing. However, some pediatric endocrinologists prime both sexes with oral estrogen preparations in order to avoid injections in boys (18, 21, 23).

Some researchers have raised concerns that the administration of sex hormones to peripubertal children artificially increases the peak GH level to normal range. Specifically, the real GH secretion in the early pubertal period may not be sufficient, in some cases, for a normal pubertal growth spurt, resulting in compromised final height. Therefore, priming, by reducing the number of nonresponders to GH testing, may lead to under-diagnosis of children with transient GH deficiency that may benefit from GH treatment (5-7, 9,10).

In conclusion: The use of priming with sex steroids prior to GH stimulation test in the peripubertal period is still controversial. Although administration of sex hormones enables to differentiate between CDGP and permanent GHD it may mask children with transient GH deficiency. If priming is deemed necessary then uniform guidelines with stringent methodological criteria should be established.

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