GROWTH AND DEVELOPMENT

Patching up a better pill for GH-deficient women

Vita Birzniece and Ken K. Y. Ho

Women with hypopituitarism treated with growth hormone (GH) traditionally receive estrogens for sex hormone replacement in tablet form. Oral estrogen therapy robs these patients of the therapeutic benefits of GH; however, the use of transdermal patches circumvents this problem. The wastage of GH therapy is even more pronounced with contraceptive doses of estrogen.

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Insulin-like growth factor 1 (IGF-1) mediates the anabolic actions of growth hormone (GH). The studies of Isotton *et al.*[1] and Phelan *et al.*[2] report that during GH therapy in women with hypopituitarism, concurrent oral estrogen treatment reduces circulating levels of IGF-1, an effect that does not occur when estrogens are delivered by a transdermal route. Isotton *et al.*[1] observed an additional effect dependent on oral administration: an almost twofold mean increase in the concentration of IGF binding protein 1 (IGFBP-1). Increased binding of IGFBP-1 to an already reduced concentration of IGF-1 could lead to a further loss of an anabolic effect mediated by GH.

In their single-center survey, Phelan *et al.*[2] observed that among 69 women receiving concurrent estrogen therapy, only 13 (19%) received this treatment via a transdermal route. Among patients who took estrogens orally, the estrogen type was equally divided between natural (conjugated equine) and synthetic (ethinyl estradiol) formulations, the latter in the form of oral contraceptive steroids. Of the patients receiving oral estrogens, IGF-1 levels were lower in those taking ethinyl estradiol than natural estrogens despite the ethinyl estradiol group receiving a much higher dose of GH. The researchers estimate that oral estrogen therapy substantially increases the annual cost of GH therapy; the additional cost is more than £6,000 per year for a patient treated with oral ethinyl estradiol versus transdermal estrogen. Thus, the route and type of estrogen dictate the benefits and cost of GH replacement therapy.

What explains the route-dependent effect of estrogen on GH action? This phenomenon results from a first-pass hepatic effect of estrogens on IGF-1 levels. A reduction in IGF-1 levels is a pharmacological consequence of liver exposure (through the portal circulation) to high concentrations of estrogens absorbed from the gut.[3] The route dependency is a reflection of a dose-dependent effect, because elevation of estrogen concentration to supraphysiological levels by transdermal delivery to peripheral blood also lowers IGF-1 levels.[4]

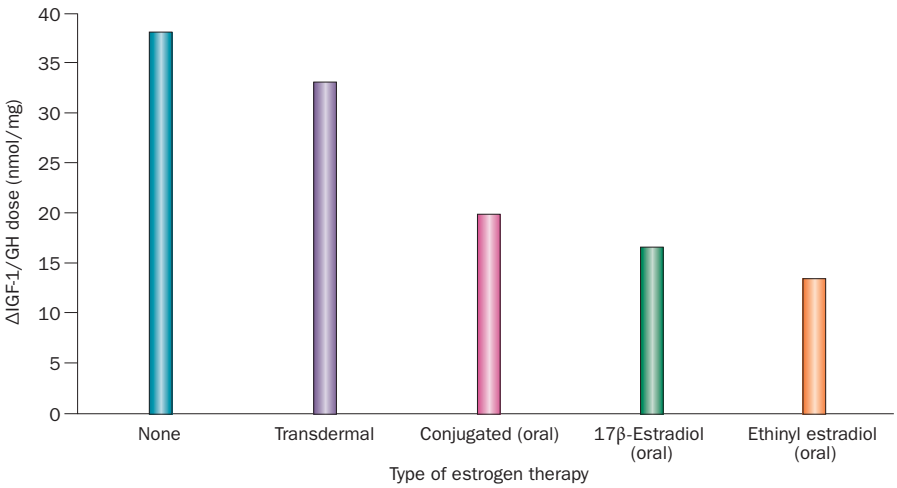

Figure 1 | The effect of route and type of estrogen therapy on the sensitivity of GH therapy in women with hypopituitarism. The GH sensitivity index was calculated as change in IGF-1 level (nmol/l) by dose of GH (mg). Created using data from four key studies.[2,5,8,10] Abbreviations: GH, growth hormone; IGF-1, insulin-like growth factor 1.

In addition to stimulating IGF-1 production, GH also stimulates hepatic lipid utilization and protein metabolism. Indeed, Wolthers and co-investigators reported that concurrent estrogen delivery by the oral but not transdermal route also attenuates fat oxidation and whole-body protein anabolism in women with hypopituitarism during GH therapy.[5] The broad effect of estrogen is a direct consequence of its inhibition of the signaling of the GH receptor.[6] The GH-regulated endocrine and metabolic function of the liver are, therefore, highly sensitive to the inhibitory effects of estrogen.

Estrogens are available in various formulations of varying potency.[7] They are widely used in two clinical settings: for replacement therapy and for contraception. Only small replacement doses are required to treat estrogen deficiency in contrast to the supraphysiological doses required to suppress the pituitary–gonadal axis for contraception. The potency and dosages used for contraception are, therefore, far higher than those required for replacement therapy, which explains why potent synthetic estrogens, such as ethinyl estradiol, are preferred contraceptive formulations. When taken, oral estrogen contraceptives exert a far greater effect on liver function than natural formulations traditionally used in replacement regimens.[7] The inappropriate estrogen regimen observed in the vast majority of patients by

Phelan *et al.*[2] is similar to that reported from a large postmarketing surveillance study. Mah *et al.*[8] observed that among 315 women with hypopituitarism taking estrogens, 86% were prescribed oral formulations, of which 30% were oral contraceptive steroids. On average, patients taking oral contraceptive pills or any oral formulation of estrogen required a 55–70% or 20–30% higher GH dose, respectively, than those using transdermal patches; furthermore, women using transdermal patches had the highest IGF-1 levels.[2,8] Figure 1 summarizes the effect on GH sensitivity of the route and type of estrogen concurrently taken, which was created using data from key studies in the literature. GH sensitivity is affected by the route of administration and the potency of prescribed estrogen.

Do selective estrogen receptor modulators (SERMs) have a role in the treatment of women with hypopituitarism? SERMs, such as raloxifene, are often used in postmenopausal women with hypopituitarism to achieve beneficial estrogen effects (for example, effects on bone). Raloxifene reduces IGF-1 levels to a lesser degree than estrogens in postmenopausal women with hypopituitarism, which suggests lesser attenuation of GH action.[9] However, in women with hypopituitarism receiving GH therapy, co-treatment with raloxifene resulted in blunted metabolic changes and reduced benefits on body composition and bone density compared with estrogen co-treatment.[10] Raloxifene, therefore, offers no advantage over estrogen to GH-deficient women during GH replacement therapy.

In conclusion, treatment of estrogen deficiency with a tablet cannot be advocated in women with hypopituitarism. This route is unphysiological and wasteful of GH treatment. The waste of GH is even greater when contraceptive instead of replacement doses of estrogen are prescribed. The prevalence of oral estrogen use in this patient group is disturbingly high. Compelling evidence-based justification exists for a change in practice by a simple switch from pill to patch. This recommendation applies equally to untreated women with hypopituitarism and GH deficiency, because oral estrogen therapy worsens the degree of GH deficiency.

*Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst, Sydney, NSW 2010, Australia (**V. Birzniece**). Centres for Health Research, Princess Alexandra Hospital, Woolloongabba, Brisbane, QLD 4102, Australia (**K. K. Y. Ho**).*
Correspondence to: K. K. Y. Ho
k.ho@uq.edu.au

Competing interests
The authors declare no competing interests.

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REPRODUCTIVE ENDOCRINOLOGY

Athletes' bodies, sexed bodies—intersexuality in athletics

Eric Vilain and Francisco J. Sánchez

In April 2011, the International Olympic Committee determined that women with hyperandrogenism and androgen levels above the lower limit of the male range cannot compete against other women. This attempt to implement a 'level playing field' has received much criticism. But is it justified?

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How much testosterone is too much testosterone for a female athlete? The International Olympic Committee (IOC) and the International Association of Athletic Federations began debating this question in January 2010 during a joint meeting in Miami, on the heels of a sensationalized story concerning a South African runner. In April 2011, the IOC released its decision in which the rules that determine whether female individuals with hyperandrogenism can compete in the female category were outlined.[1] Simply put, these individuals can compete against other female athletes if their androgen levels are below the male range.

This move is a much-improved approach to past attempts to 'level the playing field'. Since the 1930s, sex-verification tests for female athletes have run the gamut. For instance, females have paraded naked in front of judges and undergone direct physical examination. At one point the problematic sex-chromatin test, which indirectly detects the presence of two X chromosomes, was used; this approach ruled out women with chromosomal and genetic anomalies but could have ruled in men with more than one X chromosome.

Nevertheless, much criticism has been levied against the IOC's new standard.[2,3] The fairest criticism is that sex-verification policies have been and continue to be sexist: sex verification has never been conducted on male athletes. What is also true is that athletes are endowed with performance-enhancing genes that predispose them to be athletically superior. For instance, unique polymorphisms have been found among elite athletes, including variations in the *ACE* gene (which affects muscle growth and efficiency)