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Mini-Review

Managing Estrogen Therapy in the Pituitary Patient

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Abstract

Growth hormone (GH) regulates metabolic and physical health in the adult human. Because the GH system is regulated by estrogens, therapeutic estrogen compounds are likely to affect metabolic health. Estrogens are available for oral and parenteral use in natural, prodrug, and synthetic formulations including selective estrogen receptor modulators (SERMs). This review covers the pharmacology of estrogen and the effects on GH action to inform judicious use in the pituitary patient. The effects on the GH system are route dependent due to first-pass hepatic metabolism. Oral but not parenteral estrogen compounds inhibit GH action, reducing hepatic insulin-like growth factor-1 (IGF-1) production, protein anabolism, and fat utilization. In patients with GH deficiency, oral estrogen therapy exacerbates the degree of hyposomatotrophism and attenuates the beneficial effects of GH replacement therapy, effects that are greater with contraceptive than replacement doses. Surveys report that less than one-fifth of hypopituitary women are appropriately replaced by a transdermal route and up to half on oral therapy are inappropriately treated with contraceptive steroids. In acromegaly, however, estrogens, especially synthetic formulations of greater potency, reduce IGF-1, improving disease control, an effect also observed in men treated with SERMs. The route-dependent effects and potency of estrogen formulations are important considerations for optimizing the management of hypogonadal patients with pituitary disease, in particular GH deficiency and acromegaly. For hypopituitary women, estrogens should be replaced by a nonoral route. For acromegaly, oral estrogen formulations can be considered as simple adjuvant therapy for disease control.

Key Words: estrogen, IGF-1, growth hormone, pituitary, acromegaly, liver

Abbreviations: GH, growth hormone; IGF-1, insulin-like growth factor-1; IGFBP-1, insulin-like growth factor-1 binding protein; SERM, selective estrogen receptor modulator.

Growth hormone (GH) plays an important physiological role in the regulation of metabolic health and body composition in the adult human [1]. There are substantial regulatory interactions between the gonadal and the GH axes that are mediated by estrogens. Estrogen-based medications can therefore affect metabolic health though their effect on the GH axis. These effects are route dependent and matter for the patient with pituitary disease. Surveys of estrogen usage reveal a lack of awareness of pharmacodynamic effects of estrogen in clinical practice. This narrative review will cover estrogen pharmacology and metabolic sequelae arising from effects on the GH axis to inform their judicious use in the pituitary patient.

Estrogen Pharmacology

Estrogen compounds are among the most commonly prescribed medications, available in a number of formulations that can be administered by an oral or parenteral route. They are prescribed for a range of medical indications with the most common indications being replacement therapy, osteoporosis, and contraception (Table 1). The average daily production rate of 17β-estradiol, the predominant estrogen in the body, varies between 50 and 100 μg during the follicular phase, rising by more than 5-fold during mid cycle [2]. This indicates that estrogens should be replaced at a dose or dose equivalent to or approximating the daily production rate in hypogonadal women.

Replacement therapy is aimed at delivering an amount that achieves the same blood levels as what is normally produced each day. When administered by the oral route, estradiol is rapidly metabolized and inactivated by the liver. Micronized forms of 17β-estradiol or prodrug formulations such as estradiol valerate or conjugated equine estrogen have been developed to increase bioavailability. These oral estrogen formulations must be delivered at doses sufficient to overcome hepatic metabolism and attain physiological levels in the systemic circulation. For replacement therapy with 17β-estradiol, 2 mg delivered orally is equivalent to 100 μg delivered transdermally, a 20-fold difference [3, 4]. Oral delivery results in unnaturally high estrogen concentration in portal blood inducing major effects on liver function, such as the production of clotting factors [3]. Less widely known are metabolic effects arising from disruption of the GH–insulin-like growth factor (IGF) physiology (discussed later). These collective effects are circumvented by employing a nonoral route such as transdermal delivery using a skin patch.

For contraception, estrogen formulations of higher potency have been developed to suppress the pituitary-gonadal axis.

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Table 1. Estrogen pharmacology: indications, oral formulations, and doses of commonly prescribed estrogen compounds

Indication	Oral formulation or type	Daily therapy doses
Estrogen replacement	Micronized 17β-estradiol[a] Estradiol valerate Conjugated equine estrogen	1-2 mg 1-2 mg 0.3-1.25 mg
Contraception	Ethinyl estradiol	20-50 μg
Other	SERM	
Osteoporosis	Raloxifene	60 mg
Breast cancer prophylaxis	Tamoxifen	20 mg
Infertility	Clomiphene	50 mg

Abbreviation: SERM, selective estrogen receptor modulator.
[a]The average daily dose of 17β-estradiol for replacement therapy formulated in a patch delivered by the transdermal route is between 50 and 100 μg.

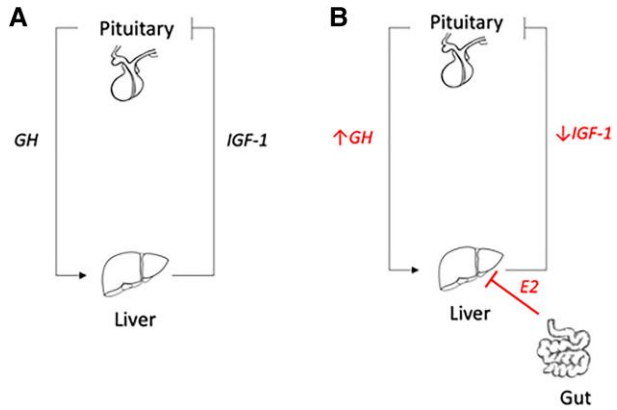

Figure 1. A, Normal physiological feedback mechanism of the growth hormone (GH) axis. B, The effect of oral estrogen administration, exposing the liver to supraphysiological levels of estrogen, subsequently reducing insulin-like growth factor-1 (IGF-1) secretion and feedback inhibition resulting in increased GH secretion.

The most widely used estrogen type is ethinyl estradiol, a synthetic estrogen resistant to hepatic metabolism. Less than 20 μg of oral ethinyl estradiol is sufficient, reflecting a potency of more than 50 to 100 times that of 17β-estradiol, imparting an even greater effect on hepatic function [4, 5].

Selective estrogen receptor modulators (SERMs) are synthetic estrogen compounds with tissue-specific agonist and antagonist actions [6]. They are prescribed in clinical practice for several conditions including ovulation induction, breast cancer, and osteoporosis. Clomiphene, raloxifene and tamoxifen are examples of SERMs in therapeutic use (see Table 1).

Estrogen and the Growth Hormone Axis

Estrogen Regulation of Growth Hormone Secretion

GH is secreted in a pulsatile manner from the anterior pituitary, stimulated by GH-releasing hormone and inhibited by somatostatin. In adults, GH is an important regulator of substrate metabolism and physical function [7–9]. There is strong evidence for a role of estrogen in the regulation of GH secretion. In the pituitary gland, somatotroph and lactotroph cells express the highest concentration of estrogen receptors [10], and in the hypothalamus estrogen receptors are widely distributed through the paraventricular nucleus, ventromedial nucleus, and lateral hypothalamus [11]. There is a close link between the GH and gonadal axis during the lifespan; during puberty, the menstrual cycle, and menopause, changes in blood estrogen levels are associated with corresponding changes in GH concentrations [12]. GH secretion increases with increasing stages of puberty in girls, especially in late puberty. During the menstrual cycle, GH levels are higher during the luteal than the early follicular phase and peak in the late follicular phase. GH levels are higher in premenopausal than in postmenopausal women. These collective observations of a strong association between estrogen and GH status at various stages of development and life suggest that estrogen positively regulates GH secretion.

Route Dependency and Mechanism

The key elements of the GH system are the secretion of GH from the pituitary gland and its feedback inhibition by IGF-1 produced from the liver by GH. Estrogen regulates a range of hepatic metabolic functions such as lipoprotein metabolism and fat oxidation. An invariant finding from studies employing estrogen treatment by the oral route is the enhancement of GH secretion triggered by a fall in circulating IGF-1, reducing negative feedback inhibition [12, 13] (Fig. 1). The attenuation of GH action arises from estrogen inhibition of hepatic GH receptor signaling, occurring in parallel with a rise in estrogen-sensitive hepatic proteins such as sex hormone–binding globulin, corticosteroid-binding globulin, thyroxine-binding globulin, and GH-binding protein [13]. The extent of IGF-1 suppression and GH stimulation is dependent on the dose and potency of oral estrogen formulation [4]. Among 3 different oral formulations, 20 μg ethinyl estradiol induced the greatest dissociation, followed by 1.25 mg conjugated equine estrogen, then 2 mg estradiol valerate in a group of postmenopausal women (Fig. 2). These changes are also reflected in the degree of gonadotropin suppression [4]. In addition to reducing IGF-1 synthesis, oral estrogen delivery also increases the concentration of IGF binding protein (IGFBP-1) [14], reducing the bioavailability and effect of already reduced IGF-1 levels. These effects do not occur with transdermal estrogen at replacement doses in postmenopausal women [5, 15]. The route-dependent phenomenon is a reflection of a concentration-dependent estrogen effect on liver function. Transdermal delivery of estrogens in supraphysiological doses that result in high levels in systemic blood impair GH action [16]. In postmenopausal women, oral estrogen therapy in replacement doses reduces insulin sensitivity, increases fat mass, and reduces lean mass compared to transdermal therapy [17, 18]. These are substantial metabolic effects that are highly relevant for the pituitary patient.

Estrogen Therapy and the Pituitary Patient

Growth Hormone Deficiency

The effect of estrogen replacement on the GH axis is particularly important in the patient with GH deficiency. GH plays an important role in reducing adipose tissue and increasing muscle mass, strength, and exercise capacity through effects on lipid oxidation, protein synthesis, and cardiorespiratory function [7–9, 19]. In women with hypopituitarism, oral estrogen therapy counteracts the benefits of GH replacement, so higher doses of GH are required to achieve equivalent

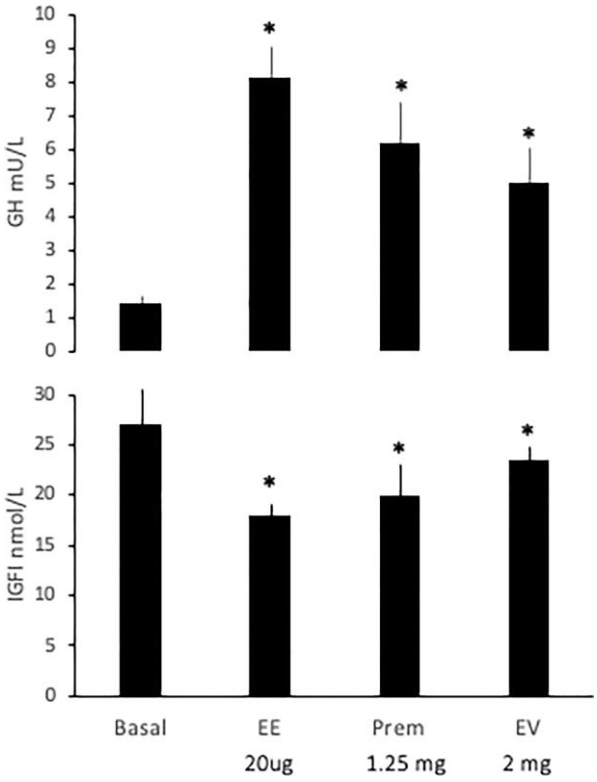

Figure 2. Mean 24 hours growth hormone (GH) and insulin-like growth factor-1 (IGF1) concentrations in postmenopausal women at baseline (basal) and after sequential randomized daily treatment with 20 μg ethinyl estradiol (EE), 1.25 mg Premarin (Prem), or 2 mg estradiol valerate (EV) showing the reduction in IGF1 and reciprocal increase in GH secretion. **P* less than .05 vs basal. Adapted from Kelly et al [4].

IGF-1 levels as those receiving transdermal therapy [20–22]. These effects are worse with oral contraceptives because of their greater potency compared to estrogens prescribed for replacement [23]. Several observational studies have reported that women require a higher dose of GH than men during replacement therapy. However, the replacement doses for GH-deficient women are lower, approximating those for men when estrogen is administered in hypopituitarism by the transdermal estrogen route [20].

Thus, for the hypopituitary woman, estrogens should be co-replaced via a parenteral route to optimize GH-replacement therapy. This recommendation is also highly relevant for the many hypopituitary patients not replaced with GH. In hypopituitary women in whom IGF-I levels are already low, oral estrogen therapy cause a further fall by as much as 30% after a standard replacement dose of 2 mg 17β-estradiol, worsening the severity of GH deficiency [21, 24]. For pituitary patients who are not GH deficient, oral estrogen replacement induces a metabolic state of GH insufficiency similar to that observed in otherwise healthy postmenopausal women. In these estrogen-deficient women, oral estrogen therapy for 6 months lowered blood IGF-1 levels and suppressed fat oxidation and protein synthesis, resulting in a loss of lean mass and a gain fat mass compared to changes observed during transdermal delivery [17]. Thus GH-sufficient female pituitary patients are also susceptible to the detrimental effects of oral estrogen therapy. The caveat concerning the route of estrogen therapy applies to all female pituitary patients but in particular to those with GH deficiency.

Estrogen prescribing in clinical practice

While the importance and rationale for prescribing the appropriate estrogen formulation for patients receiving GH replacement is established, the question as to whether this knowledge is translated to clinical practice has been investigated. In a UK study involving more than 300 estrogen-treated hypopituitary women, Mah et al [25] reported that the vast majority (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% to 70% or 20% to 30% higher GH dose, respectively, than those using transdermal patches. Another study also from the United Kingdom observed that among 69 hypopituitary women treated with estrogens, only 19% were prescribed transdermal formulations [26]. Among patients who took estrogens orally, the estrogen type was equally divided between conjugated estrogens and contraceptive steroids. Both studies observed that in patients receiving oral estrogens, IGF-1 levels were lower with contraceptive formulations than with conjugated estrogens in replacement doses despite the ethinyl estradiol groups receiving a much higher dose of GH. As illustrated in Fig. 3A and 3B, the distribution of estrogen prescriptions shows that less than one-fifth of hypopituitary women receive appropriate therapy via the transdermal route. Among the vast majority receiving oral therapy, more than half are prescribed estrogens in contraceptive doses. Phelan et al [26] have estimated that oral estrogen therapy substantially increased the annual cost of GH therapy by more than £6000 per year compared to that of transdermal therapy. These 2 surveys reveal a lack of judicious prescription of estrogens in the management of women with hypopituitarism [23].

Selective estrogen receptor modulators

There is limited knowledge of the effect of SERMs on hepatic modulation of metabolism by GH. They are largely prescribed for the management of infertility, osteoporosis, or hormone-responsive breast cancers. In female patients with pituitary disorders, they are likely prescribed for osteoporosis to patients with low preference for or unable to tolerate estrogens. Our laboratory has investigated whether SERMs offer any advantage over oral estrogen therapy in conventional therapy doses of 2-mg estradiol valerate and 60-mg raloxifene.

In hypopituitary women with untreated GH deficiency, estradiol valerate and raloxifene reduced IGF-1 and fat oxidation equally [24]. During GH replacement, estradiol valerate and raloxifene both attenuated the increase of IGF-1 by the same degree. However, raloxifene inhibited fat oxidation and protein anabolism to a greater extent [27]. Over 18 months of GH replacement therapy, cotreatment with estradiol valerate increased lean mass and bone mass and reduced fat mass to a greater extent than with raloxifene [28]. The observations with raloxifene indicate that SERMs offer no benefit over estrogens during GH-replacement therapy. Transdermal estrogens should be the first choice of therapy in patients requiring concurrent estrogen and GH-replacement therapy.

Acromegaly

The inhibitory effects on GH action suggests that oral estrogen and SERMS may be useful adjunctive therapy in acromegaly. Estrogens were noted to improve clinical signs and

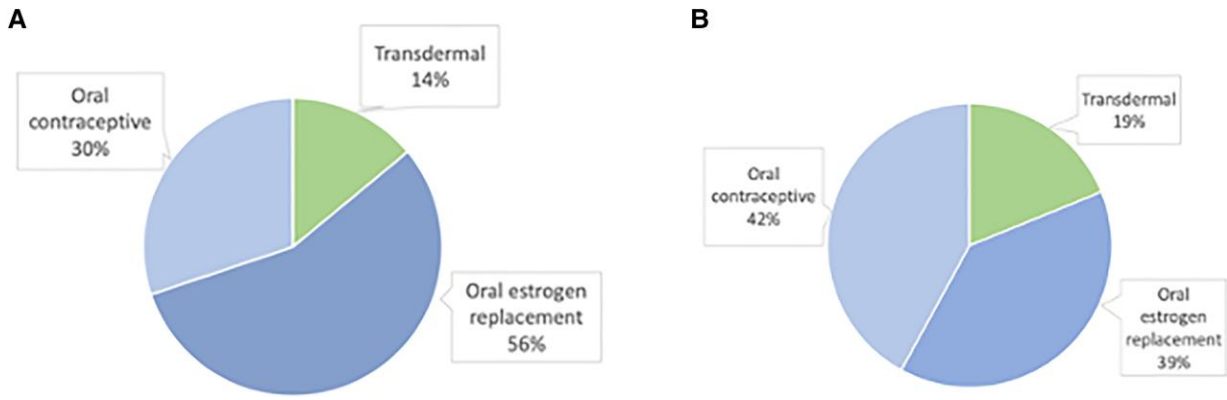

Figure 3. Prescription of estrogen therapies in hypopituitary women in 2 surveys: A, consisting of 315 women [25] and B, consisting of 69 women [26]. The figures show the proportions that were prescribed transdermal estrogens and oral estrogens either in replacement doses or in contraceptive doses. Refer to text for details.

Table 2. A summary of studies reporting the successful use of estrogens and selective estrogen receptor modulators in reducing insulin-like growth factor-1 levels of acromegalic patients

Study	Patients	Estrogen type	Dose	Treatment duration	Outcomes
Magalhães et al [31]	8 women	Ethinyl estradiol	30 μg	6 mo	IGF-1 decreased in 5, normalized in 3
Shimon and Barkan [32]	3 women	Ethinyl estradiol	20 and 35 μg	Not stated	IGF-1 decreased in all
Cozzi et al [33]	8 women	Ethinyl estradiol	30-40 μg/d	13 mo (mean)	IGF-1 decreased in 6, normalized in 4
Cozzi et al [36]	6 men 13 women	Tamoxifen	20-40 mg/d	2 mo	IGF-1 decreased in 13
Maiza et al [37]	1 woman	Tamoxifen	20 mg/d	13 mo	IGF-1 decreased
Attanasio et al [38]	13 women	Raloxifene	60 mg/d	5.2 mo (mean)	IGF-1 decreased in 10
Dimaraki et al [39]	8 men	Raloxifene	120 mg/d	5 wk (median)	IGF-1 decreased in all
Duarte et al [40]	16 men	Clomiphene citrate	50 mg/d	3 mo	IGF-1 decreased in all, normalized in 7

Abbreviation: IGF-1, insulin-like growth factor-1.

symptoms in patients with acromegaly in the 1940s, long before the pathophysiology of acromegaly was understood and before IGF-1 was discovered or measurable. Oral estrogen therapy improved control of diabetes, pain, fine motor movements, and strength, reducing hand size and excessive diaphoresis [29, 30]. The estrogens prescribed were stilbestrol in doses from 10 to 60 mg daily and ethinyl estradiol in doses from 0.15 to 5.0 mg daily. Stilbestrol is no longer available.

A number of recent studies have explored the efficacy of both estrogens and SERMs in the treatment of acromegaly, summarized in Table 2. These studies report significant reduction in IGF-1 levels when either treatment option was used as adjuvant therapy alongside conventional therapy or in some cases solo therapy. From the 3 studies using estrogen at contraceptive doses, 14 of 19 patients showed reduction in IGF-1 level [31–33]. Tamoxifen reduced IGF-1 level in 70% of 20 patients, raloxifene in 86% of 21 patients, and clomiphene citrate in all 16 patients (see Table 1). These studies have not reported symptomatic, metabolic, or clinical changes. Nevertheless, the findings from these small, uncontrolled observational studies provide persuasive evidence supporting the use of both estrogens and SERMS as low-cost and effective options for the treatment of acromegaly in women and men. While promising, prospective controlled studies on safety and efficacy are required to inform the place of estrogens in the treatment of acromegaly. Estrogen therapy is not discussed in the guidelines for the management of acromegaly of professional societies [34, 35].

Summary

Estrogen-based medications affect metabolic health in women by inhibiting GH action. These effects are route and dose dependent, acting at the liver via a first-pass effect reducing IGF-1 production, protein anabolism, and fat utilization. These effects are particularly pertinent for hypopituitary women, because oral estrogen therapy worsens the degree of GH deficiency, and attenuates the cost and therapeutic benefits of GH-replacement therapy, effects that are more severe with contraceptive doses. Surveys reveal that less than 20% of hypopituitary women receive appropriate estrogen prescriptions in clinical practice. In acromegaly, oral estrogen–based medication including oral contraceptive steroids and SERMs improve or normalize biochemical control. Estrogens are not yet widely used nor discussed in the guidelines for the management of acromegaly of professional societies.

Conclusion

The pharmacodynamics of therapeutic estrogen compounds on GH biology is well established but not sufficiently

appreciated nor translated into the clinical management of patients with pituitary disorders. We strongly recommend that hypopituitary women requiring estrogens be treated with transdermal formulations. In acromegaly, oral estrogen–based medications including SERMs should be considered as simple and inexpensive adjuvant treatment for disease control.

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Disclosures

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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