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Androgen Replacement Therapy in Androgen-Deficient Women with Hypopituitarism

Hong Zang[1] and *Susan R. Davis*[2]

1 Department of Obstetrics and Gynecology, The First Affiliated Hospital, Dalian Medical University, Dalian, Liaoning, China
2 Women's Health Program, Department of Medicine, Monash University, Prahran, Victoria, Australia

Abstract

Hypopituitarism is a rare disorder, but its prevalence has increased as a result of an increase in secondary causes of hypopituitarism such as traumatic brain injury and cranial irradiation. Estrogen with or without progestogen (progestin) treatment is conventional therapy in women with hypopituitarism. Recent data demonstrate that women with hypopituitarism may experience marked androgen deficiency as a consequence of secondary loss of function of the adrenal cortex and/or ovaries. This deficiency is not always considered and therefore androgen therapy is not routinely prescribed. Recent clinical trials indicate that testosterone supplementation in physiological doses for androgen-deficient women with hypopituitarism may improve psychological well-being and sexual function, and increase bone mineral density and lean body mass. Dehydroepiandrosterone (DHEA; prasterone) supplementation may be an option for women with hypopituitarism who have secondary adrenal insufficiency and low levels of DHEA and DHEA sulfate. While short-term treatment with testosterone or DHEA appears to be safe, long-term safety data are lacking. Androgenic adverse effects limit the acceptability of treatment for some women. Further studies to establish the efficacy and safety of androgen treatment for long-term intervention in a larger group of hypopituitary androgen-deficient women are needed.

1. Hypopituitarism

Hypopituitarism is the partial or complete insufficiency of hormone secretion from the anterior pituitary. This may involve insufficient production of adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), growth hormone (GH) and/or prolactin. Hypopituitarism may be primary or secondary to hypothalamic-releasing hormone insufficiency.

The incidence of hypopituitarism is approximately 4.2 per 100 000 per year with no gender difference. In a population-based study, the most common causes of hypopituitarism were pituitary tumours (61%), non-pituitary tumours (9%) and non-tumour causes (30%), including idiopathic cases (11%) and Sheehan's syndrome (6%).[1] Recent studies indicate that traumatic brain injuries and cranial irradiation contribute to an increased prevalence of hypopituitarism.[2,3]

Hypopituitarism can be an isolated or involve multiple defects of the hypothalamic-pituitary axes. Clinical manifestations of hypopituitarism are variable, often non-specific and insidious at onset, depending on the extent and variety of hormone deficien-

cies.[4] ACTH, TSH and antidiuretic hormone (ADH) deficiencies are potentially life-threatening if they are not diagnosed and treated early.[5,6] Gonadotropin (LH/FSH) and GH deficiencies cause chronic morbidity. Life expectancy is reduced in individuals with hypopituitarism, with increased rates of cardiovascular and cerebrovascular deaths compared with an unaffected population contributing primarily to this increased mortality.[7] In addition to addressing the aetiology of hypopituitarism, replacement of deficient hormones is required for affected individuals and life-long follow-up is essential.

1.1 Hormone Replacement Therapy in Patients with Hypopituitarism

The aims of hormone replacement therapy for individuals with hypopituitarism are to achieve normal levels of circulating hormones in order to restore normal physiology, with minimal adverse effects. However, the pharmacological and pharmacokinetic properties of available hormone preparations in clinical practice do not yet meet these goals.

In hypopituitary patients, loss of pituitary hormone secretion may follow a sequential pattern. Classically, there is a decline in GH followed by the gonadotropins, TSH, ACTH and, finally, prolactin.[1] Target hormones are administered for specific deficiencies; glucocorticoids for ACTH deficiency, levothyroxine for TSH deficiency, and testosterone (in men) and estrogen and progestogen [progestin] (in women) for gonadotropin deficiency. In general, testosterone treatment of men is life-long, whereas in women, use beyond the average age of menopause is on a case-by-case basis. When fertility is desired in a woman, cyclical gonadotropin therapy is administered.[4] In patients with multiple pituitary hormone deficiencies, there are potential interactions between the exogenous hormone treatments, such as between oral estrogen and both GH and levothyroxine, and between GH and levothyroxine. Therefore, the order and dose titration for the replaced hormones are of clinical importance.

Although some patients have total failure of pituitary function, often only one or two hormones are deficient. The most common selective deficiencies are those of GH and/or gonadotropin.[4] Gonadotropin deficiency was reported in 87% of individuals with hypopituitarism in a population-based study.[1] Gonadotropin deficiency in women results in loss of ovarian function and hence anovulation, oligomenorrhoea, urogenital atrophy, breast atrophy, loss of libido and bone loss. Moreover, psychological well-being is decreased in affected women.[8] For women with hypopituitarism, treatment of gonadotropin deficiency is conventionally by estrogen plus progestogen therapy, or estrogen alone in hysterectomized women. In general, the duration of estrogen-progestogen therapy should be at least until a woman has reached the average age of menopause (51 years).[9] Beyond that, continuation of therapy involves addressing the needs of each woman and weighing her risks and benefits of ongoing treatment. Although some studies have suggested estrogen-progestogen treatment improves quality of life (QOL),[10] others suggest that this is incomplete hormone replacement for younger women.[11] Recent evidence suggests that loss of ovarian and adrenal androgen production in women with hypopituitarism has clinical sequelae that impact on QOL.[11]

This article reviews the evidence that androgen replacement should be considered for androgen-deficient women with hypopituitarism.

2. Should Women with Hypopituitarism Undergo Androgen Replacement Therapy?

2.1 Androgen Production and Actions

The main pre-androgens, produced by the ovaries and the adrenal glands in women,[12,13] listed in descending order of their serum concentrations, include dehydroepiandrosterone (DHEA) sulfate (DHEAS), DHEA and androstenedione. These precursors are the source of extra-gonadal production of the potent androgens, testosterone and dihydrotestosterone (DHT). About 25% of circulating testosterone is secreted directly by the ovaries. The remainder is from peripheral conversion of the pre-androgens. Testosterone is irreversibly converted to the potent DHT via 5α-reductase or to estradiol by aromatase in peripheral tissues.

The biological roles of androgens in women are incompletely understood. Their actions in multiple organs are supported by the presence of androgen

receptors in various tissues, including bone, skeletal muscle, adipose tissue, skin, brain, breast, heart and the genitourinary tract.[14] Beneficial effects of androgen treatment on psychological well-being and sexual function may be related to their actions on the CNS and the genital tract.[15-17] Androgens have positive effects on bone and muscle mass by stimulating bone formation and protein synthesis.[18,19] Although evidence exists for short-term efficacy of androgen treatment on well-being, sexual function and bone mass in surgically and naturally postmenopausal women,[20] the long-term safety of androgen treatment on the breast, endometrium and cardiovascular function is unresolved.[21]

2.2 Androgen Deficiency in Women with Hypopituitarism

Serum concentrations of total testosterone, free testosterone, DHEAS and androstenedione decline steeply with age in women. The decline in testosterone is greatest in the early reproductive years, such that testosterone levels in women aged 40 years are approximately half those of women aged 20 years.[22,23] In contrast, DHEAS declines linearly with age from the 20s through to the late 70s.[22] Menopausal status does not influence androgen levels, with no change in androgens reported across the years of menopausal transition.[22] The circulating testosterone levels are about 50% lower in oophorectomized versus non-oophorectomized women.[22,24] This decrease in androgen levels may be associated with sexual problems and a decrease in psychological well-being.[25,26] Total testosterone levels are significantly lower in premenopausal and postmenopausal women with hypopituitarism due to loss of both ovarian and adrenal androgen production.[27] DHEAS levels are also lower in the combined group of hypopituitary women and men.[28,29]

Miller and colleagues[11] investigated androgen levels in hypopituitary women with hypogonadism and/or hypoadrenalism. They reported that serum levels of testosterone, free testosterone, androstenedione and DHEAS were markedly lower in both premenopausal and postmenopausal hypopituitary women compared with healthy controls, regardless of whether or not women were receiving concurrent estrogen replacement. Furthermore, serum concentrations of testosterone, free testosterone and androstenedione were lower in women with both hypogonadism and hypoadrenalism than in women with either hypoadrenalism or hypogonadism. DHEAS levels were lower in the hypopituitary women with combined hypogonadism and hypoadrenalism than in women with hypogonadism alone, indicating specific impact of loss of DHEAS production by the adrenal glands.[11]

2.3 Estrogen-Progestogen Replacement in Women with Hypopituitarism

Estrogen therapy is standard for hypopituitary women with gonadotropin deficiency for short-term relief of symptoms (loss of libido, decrease of well-being and dyspareunia) and for long-term prevention of osteoporosis.[30] Although oral contraceptives containing ethinyl estradiol 20–35 μg are often prescribed, these women are not in need of contraception. Hence, lower dose treatment with 17-β estradiol is the preferred therapy, with or without progestogen depending on hysterectomy status. Transdermal estradiol administration has several advantages: (i) it does not decrease insulin-like growth factor-1 levels and therefore does not alter the dosage of GH substitution;[31] (ii) it does not increase sex hormone-binding globulin levels and hence does not further lower circulating free testosterone; (iii) it does not alter thyroid-binding globulin levels, as does oral estrogen, and thus will not require levothyroxine dose adjustment;[32] (iv) it is associated with a significantly lower risk of thromboembolic disease.[33]

3. Testosterone Replacement in Women with Hypopituitarism

Testosterone supplementation has been used for the treatment of loss of libido in women.[34] Transdermal testosterone in the form of a transdermal patch is approved in the EU for surgically menopausal women with persistent loss of libido, despite adequate estrogen therapy using non-conjugated equine estrogens. Studies indicate that the administration of various preparations of testosterone, including intramuscular injection, subcutaneous implants and oral tablets, improves sexual function and psychological well-being in naturally and surgically menopausal women,[35-37] and in premenopausal

women.[38,39] Although older studies investigated doses that resulted in supraphysiological and unpredictable testosterone levels,[35-37] more recent studies have involved doses of testosterone that achieve circulating free testosterone levels found in young healthy women.[39,40] The positive effects on sexual function and psychological well-being reported in these studies appear to be mediated via androgen action.[17] In combination with estrogen, testosterone therapy also appears to have positive effects on bone mineral density[41,42] and body composition.[43,44] Exogenous testosterone increases lean body mass (fat-free mass) and muscle strength in postmenopausal women.[44]

Recent clinical practice guidelines provide conflicting recommendations regarding the use of testosterone therapy for women.[21,45] However, hypopituitarism is an accepted cause of androgen deficiency and the hypopituitary androgen-deficient women may benefit from androgen replacement.

Data reporting the effects of androgen replacement therapy in women with hypopituitarism are limited.[46] In a randomized, double blind, placebo-controlled study, 51 hypopituitary women of reproductive years were treated with transdermal testosterone (300 μg/day) or placebo for 12 months. After testosterone administration, free testosterone levels increased into the normal range for premenopausal women, and mood, sexual function and the some aspects of QOL were significantly improved.[47] Dual x-ray absorptiometry demonstrated that bone mineral density in the hip and radius increased significantly more in the group receiving testosterone, as did lean body mass. There were no changes in intra-abdominal and subcutaneous fat mass when measured by CT scan.[47]

Concerns have been raised regarding potential adverse metabolic effects of androgen therapy. Studies of treatment with oral methyltestosterone or testosterone undecanoate alone have demonstrated adverse effects on insulin sensitivity and lowering of high-density lipoprotein (HDL)-cholesterol levels.[20,48,49] Studies of non-oral testosterone therapy in the form of a transdermal gel,[17] a patch[40,50,51] or a transdermal skin spray[39] have reported no adverse effects on lipid profiles, fasting insulin or glucose, and other cardiovascular risk markers. A randomized clinical trial of hypopituitary women reported that insulin resistance, determined by a homeostasis model of assessment, was significantly lower in the testosterone-treated women than in the placebo group.[52] HDL cholesterol levels were not decreased by the dose of testosterone used and markers of increased cardiovascular risk, including high-sensitivity C-reactive protein, vascular cell adhesion molecule, leptin, lipoprotein (a), apolipoprotein A1 and homocysteine, were unaffected.[52] The frequency of androgenic adverse effects was comparable in both treatment groups. Thus, although androgen therapy with supraphysiological doses results in adverse metabolic effects in women, this does not appear to be the case with physiological therapy for androgen-deficient women.[53] Short-term studies do not indicate an adverse effect of testosterone on the breast[54,55] or the endometrium.[56] The long-term effects of exogenous testosterone on the breast and the endometrium are not known.[57,58]

In summary, as in studies with healthy women, transdermal testosterone treatment of women with androgen deficiency, secondary to hypopituitarism, has beneficial effects on QOL, sexual function, bone density and body composition, and does not appear to lower HDL cholesterol or affect other cardiovascular risk factors. More studies to establish such effects and the long-term safety of testosterone treatment in androgen-deficient women with hypopituitarism are warranted.

4. Dehydroepiandrosterone (DHEA) Replacement Therapy

Whereas evidence to support the use of DHEA (prasterone) therapy in healthy women is inconsistent, several studies have demonstrated benefits of DHEA for sexuality and general well-being in women with adrenal insufficiency.[59]

4.1 DHEA Replacement in Women with Adrenal Insufficiency

Adrenal insufficiency is characterized by abnormally low, sometimes undetectable, serum concentrations of DHEA and DHEAS. Treatment with DHEA 50 mg/day raises the serum concentrations of DHEA, DHEAS, androstenedione and testosterone into the low normal or normal range for women with

adrenal insufficiency.[60,61] Several studies have examined the effects of DHEA replacement on sexual function and/or well-being in women with adrenal insufficiency but results were conflicting.[60-64]

Arlt et al.[60] conducted a study in 24 women, aged 23–59 years with primary and secondary adrenal insufficiency. In this double-blind, crossover clinical trial, the women were randomized to treatment with DHEA 50 mg/day or placebo for 4 months. DHEA administration significantly improved sexual function in aspects of sexual thought, interest and satisfaction, as well as well-being, with a decrease in depression and anxiety. In another double-blind, crossover study, Hunt and colleagues[61] used DHEA 50 mg/day or placebo for 3 months in a combined group of 24 women and 15 men aged 25–69 years with Addison's disease. Psychological assessment revealed significant enhancement of well-being, self-esteem, mood and a decrease in fatigue in both sexes; however, sexual function was not influenced with DHEA replacement. Furthermore, Gurnell et al.[64] investigated the effects of long-term DHEA replacement in a mixed group of 62 women and 44 men aged 22–65 years with Addison's disease in a double-blind clinical trial. After a 12-month treatment period, the emotional dimension in health status assessment was significantly improved but sexual function was not influenced. The treatment exhibited beneficial effects on bone mass at the femoral neck and total lean body mass.

In contrast, other clinical trials did not find positive effects of DHEA replacement on either psychological well-being or sexual function in women with adrenal insufficiency. van Thiel et al.[63] evaluated the effects of DHEA 50 mg/day in addition to recombinant GH in 15 men and 16 postmenopausal women with secondary adrenal failure in a crossover, double-blind study. The women in this study were estrogen depleted. After 4 months of treatment, the authors found no substantial improvement associated with DHEA treatment on either QOL or sexual function, regardless of gender. Lovas and colleagues[62] conducted a clinical trial with a parallel-group comparison in 39 women aged 18–70 years with primary or secondary adrenal failure. The women were randomized to treatment with DHEA 25 mg/day or placebo for 9 months. The levels of DHEAS, androstenedione and testosterone rose to the normal reference range for women during active treatment. However, there were no beneficial effects of DHEA replacement on the subjective health status and sexual function observed. As acknowledged by the authors, a benefit may not be excluded as the study was under powered.

4.2 DHEA Replacement in Women with Hypopituitarism

Only a few studies reported the effects of DHEA treatment on psychological well-being and sexual function in androgen-deficient women with hypopituitarism.[65,66] In a randomized, placebo-controlled, double-blind study, Johannsson et al.[66] used a low dose of DHEA (30 mg/day for those aged less than 45 years [n = 9] and 20 mg for those aged older than 45 years [n = 29]) or placebo in 38 women with hypopituitarism for 6 months, followed by a 6-month open treatment period. The administration of DHEA raised the serum levels of DHEAS to normal age-related reference ranges, but increased androstenedione and testosterone levels remained subnormal. After 6 months of blinded treatment, positive effects of DHEA on QOL were reported by the partners. Increased sexual interest and activity were reported by the women only during the open-label phase. Lean body mass was not affected by DHEA treatment during the blinded treatment period, but increased by the end of the open-label phase. Bone mineral density and serum bone markers were unchanged.

In a recent study with a similar design, 30 women aged 18–64 and 21 men with hypopituitarism receiving established GH replacement therapy, were randomized to DHEA 50 mg/day or placebo for 6 months, followed by an open-label phase of 6 months of DHEA treatment. After the initial 6 months of DHEA treatment, serum DHEAS, androstenedione and testosterone levels were in the normal range. Psychological well-being was significantly improved in the women with DHEA treatment, even after excluding those women who were estrogen deficient and who were not receiving estrogen therapy. An increase in sexual thoughts in the women who were treated was also reported.[65]

There are also concerns regarding potential metabolic effects of DHEA treatment in terms of lipids,

insulin sensitivity and cardiovascular function in women with androgen deficiency. DHEA replacement in women with adrenal insufficiency in one study led to a decrease in HDL cholesterol by up to 14%.[60] Dhatariya et al.[67] studied the effect of DHEA replacement on insulin sensitivity in 28 hypoadrenal women in a randomized, double-blind, placebo-controlled, crossover clinical trail. They reported that insulin sensitivity, assessed by euglycaemic hyperinsulinaemic clamp, was increased after 3 months of DHEA treatment, suggesting that DHEA replacement could have a potential beneficial effect. Christiansen and colleagues[68] examined the effects of DHEA replacement on cardiovascular function in ten women with adrenal insufficiency and found no deleterious effects on cardiovascular parameters and endothelial function after 6 months of active treatment.

It has been reported that the frequency of androgenic adverse effects was significantly higher in DHEA than placebo groups in several studies.[60,62,65,66] Treatment of DHEA 50 mg/day in some women with androgen deficiency led to greasy skin, acne and an increased growth of body hair.[60,65] Increases in sweat odour and scalp itching have been reported in hypopituitary women after treatment with DHEA 25 mg/day.[62,66]

In summary, two randomized, clinical studies have demonstrated that oral DHEA has beneficial effects on psychological well-being and sexual function in androgen-deficient women with hypopituitarism. Not all investigators have found beneficial effects of DHEA in women with adrenal insufficiency. This may reflect the fact that these studies were under powered and/or of short treatment durations. In addition, the different instruments employed for the assessment of QOL and sexual function in the different studies may have led to the variable results. A factor may also be the inability to identify the most appropriate women for whom DHEA treatment would be effective, for example, younger versus older women. Alternatively, DHEA may not be effective therapy for these women.

5. Androgen Preparations

Several formulations and modes of testosterone have been studied for treatment in women to improve libido and well-being. Optimal doses for treatment in women need to be determined in order to obtain beneficial effects without exceeding physiological levels and to limit androgenic adverse effects. As few products have been approved, and approval is limited to a small number of countries, it is not possible to provide detailed treatment guidelines.

Intramuscular injections of testosterone esters (50–100 mg every 4–6 weeks) result in high peak serum concentrations of testosterone and increase the risk of adverse effects and accumulation, and are not recommended.[69] The subcutaneous administration of testosterone as testosterone implants (50–100 mg every 3–6 months) provides a slow release with great individual variations in absorption.[41] Therefore, it is necessary to carefully monitor serum testosterone concentrations before and after insertion of the implant. These implants are available for postmenopausal women in the UK.[70]

There are several oral preparations of testosterone available. In the US, low doses of methyltestosterone (1.25–2.5 mg/day) combined with esterified estrogen (0.625 or 1.25 mg) are used for treatment in women. However, there are no routine methods to measure methyltestosterone in the serum. Micronized testosterone has also been used, but this preparation is largely inactivated in the liver and is therefore not an optimal formulation. Testosterone undecanoate (40 mg/day) is another oral preparation, which is absorbed via the lymphatic intestinal system and therefore avoids first-pass metabolism in the liver.[71] This preparation is available in Europe and Canada.[70] There are considerable intra- and inter-individual variations of serum testosterone concentrations seen with testosterone undecanoate.[72] These oral preparations are associated with a decrease in HDL cholesterol levels.

Transdermal testosterone preparations, both gels and patches, have been available for treatment in men for many years. In recent years, a testosterone patch (applied twice weekly to deliver 300 μg/day) has been developed for treatment in women.[73] Testosterone levels are increased to the upper normal range by 300 μg/day in oophorectomized women.[73] Testosterone patches are approved only in Europe for surgically menopausal women who have hypoactive sexual desire disorder, despite adequate estrogen treatment.

DHEA is rapidly converted to androgens and estrogens after administration.[74] Oral DHEA 50 mg/day, leads to an increase in the circulating testosterone levels to the normal range in women with hypopituitarism,[28,65] and it induces a decrease in HDL cholesterol levels. In the US, DHEA is available over the counter as a nutritional supplement.

6. Conclusions

Estrogen-progestogen therapy is standard in young women with hypopituitarism. However, many of these women still experience poor QOL, despite this conventional hormone treatment. Although severe androgen deficiency commonly coexists, androgens are not routinely replaced.

Various preparations of testosterone, including oral tablets, intramuscular injections and subcutaneous implants, provide beneficial effects in postmenopausal women, but result in supraphysiological levels of testosterone. Oral testosterone therapy is also associated with an adverse lipid profile. A transdermal testosterone patch providing physiological levels of testosterone for young women has restricted approval in Europe, and other transdermal preparations are undergoing evaluation in clinical trials. Recent clinical practice guidelines do not recommend the generalized use of testosterone by women because the indications remain poorly defined and long-term safety data are lacking.

Nevertheless, recently available evidence from randomized clinical trials demonstrates that androgen replacement with a physiological dose of testosterone or DHEA in women with hypopituitarism improves psychological well-being and sexual function, and increases bone and lean body mass without adverse metabolic effects. Therefore, hypopituitary women may benefit from androgen replacement therapy. Hypopituitarism in women with androgen deficiency is a condition that merits attention and further research to evaluate the effects of testosterone in this subset of women is warranted.

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Correspondence: Dr *Hong Zang*, Department of Obstetrics and Gynecology, The First Affiliated Hospital, Dalian Medical University, 222 Zhongshan Road, Dalian, Liaoning 116011, China.
E-mail: hzang@hotmail.com

