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Understanding Hormonal Therapies: Overview for the Dermatologist Focused on Hair

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Abstract
Hormones have an intimate relationship with hair growth. Hormonal replacement therapy is used to treat menopausal symptoms and to provide protection from chronic diseases for which postmenopausal women may be at risk. Additionally, hormonal therapies are prescribed for contraception and treatment of acne. Considering the widespread use of such therapies, there is a demand for further understanding of their implications in hair disorders. This article reviews the specific properties of current estrogen- and progesterone-containing hormonal treatments and their implications for the patient with hair loss. The complexity of the task comes from the paucity of data and discrepancy in the literature on the effect of the specific hormonal-receptor activities.

Introduction

Hormonal therapies containing estrogen and/or progestogens are frequently used in women for menopausal symptoms, contraception, and acne. A common scenario in the trichology clinics is a female patient with telogen effluvium or androgenetic alopecia on a birth control therapy or hormonal replacement therapy (HRT) asking if they can safely continue the hormonal therapy, or they need to switch or discontinue it since they are highly concerned about the progression of hair loss. Hormones have an intimate relationship with hair growth [1]. The objective of this review is to make dermatologists and particularly trichologists familiar with the specific properties of current estrogen- and progesterone-containing hormonal treatments and their implications for the patient with hair loss.

The collected information presented here was retrieved from a literature search of PubMed/MEDLINE that included studies, reviews and case reports/series addressing hormonal therapies and hair loss. MeSH terms and phrases used in various combinations in the literature search included: hormone, hair, follicle, progesterone, progestogen, progestin, estrogen, estradiol, hormonal replacement, birth control, alopecia and androgen. 44 relevant articles (excluding drug package inserts) published in English within the last 25 years were included. Our analysis shows that there is paucity of data on the risks/benefits of hormonal therapies with regard to hair loss and moreover there is discrepancy on the effect of the specific hormonal activities as outlined below.

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Main Findings

Basic Terminology

Hormonal activity is the modulation of a specific receptor by effector molecules. Binding of steroid hormones (including progesterone, androgens, estrogens, glucocorticoids and mineralocorticoids) to their receptors induces a conformational change in the receptors, which subsequently serve as transcription factors and regulate gene expression [2–4].

Progestational activity refers to induction of a secretory endometrium to support gestation [5]. Progesterone receptors are additionally present in the mammary gland, brain, pituitary gland and immune cells [5]. The term "progestogen" refers to compounds with progestational activity [5].

Androgenic and *estrogenic activities* involve the development and maintenance of male and female sexual characteristics, respectively. Estrogen has important uterotropic effects and induces a specific growth pattern of the endometrium. In scientific studies, the weight of reproductive organs (prostate/seminal vesicles for males and uterus for females) has been used to measure estrogenic and androgenic activity [2]. Androgen receptor (AR) and estrogen receptors (ER) are also expressed in many other tissues including muscle, bone, gastrointestinal tract and skin [2, 5, 6]. Moreover, two principal isoforms of ER (ER-α and ER-β) have distinct, tissue-dependent expression and functions [5, 6]. Thus, androgens/estrogens can have diverse and nuanced effects, unrelated to virilization and feminization.

Glucocorticoid activity refers to a variety of functions, ranging from metabolism to inflammation. Glucocorticoid receptors (GR) are ubiquitously expressed, with particular prominence in immune-function cells [3, 5].

Mineralocorticoid activity refers to maintaining fluid and electrolyte balance [5]. Mineralocorticoid receptors (MR) are present in many tissues, including throughout the cardiovascular system, kidney, central nervous system and adipocytes [5].

Estrogen- and Progesterone-Containing Therapies

Hormone-containing therapies used for menopausal symptoms or contraception may involve estrogen or progestogens, or both. Some combined oral contraceptives (COCs) have been approved by the US Food and Drug Administration (FDA) to treat acne in women who also desire contraception [7, 8]. Caution must be exercised when prescribing hormonal therapies as both estrogens and progestogens have been associated with increased risk of cardiovascular events, venous thromboembolic events, stroke and breast cancer [8–12]. Unopposed systemic estrogen therapy confers an increased risk for endometrial cancer. Therefore, progestogen therapy is given to prevent the overgrowth of endometrium and development of endometrial cancer in a patient who has a uterus and is taking systemic estrogen [5, 9, 12, 13]. Another option is to combine estrogen with bazedoxifene, a selective estrogen receptor modulator (SERM) that creates a tissue-selective estrogen complex [9]. Systemic estrogen therapy may be given alone in a woman without a uterus [10]. Progestogen therapy may be given alone for the purpose of contraception.

While the intended actions of prescribed estrogens and progestogens are executed through their interactions with the estrogen and progesterone receptors, respectively, hormonal therapies may exhibit off-target activities through their interactions with other steroid hormone receptors [5]. The clinical profile of combined hormonal therapies is mostly attributed to the pharmacodynamics of the particular progestogen since the dosages of the estrogen have been reduced over the years to minimize the risk of adverse events [2].

Estrogens

Systemic estrogens can be prescribed as oral drugs, transdermal patches, sprays, gels or vaginal rings. The *estrogens* most commonly prescribed are equine estrogens, synthetic conjugated estrogens, micronized 17β-estradiol and ethinylestradiol [9].

Progestogens

Progestogens are available as oral drugs, combination patches with estrogen, intrauterine devices (IUDs), implants, injectables and vaginal gels/tablets. Progestogens are subdivided into two types: natural progestogen (progesterone itself) and synthetic progestogens (collectively known as progestins). Synthetic progestins are further classified based on their structural similarity to either testosterone, progesterone or spironolactone [5, 14, 15], and they pertain to one of four "generations" [2, 4, 8, 16] (Table 1).

Many progestogens interact variably with other members of the steroid receptor family, including the AR, GR and MR [5]. Progestogens can elicit various activities by binding to the AR, ranging from no effect to agonist, partial agonist and antagonist activity. The antiandrogenic effects of several progestins such as dienogest or cyproterone acetate are not ascribed solely to binding of AR, but also to competitive inhibition of 5α-reductase activity, thereby decreasing the conversion of testosterone to the more active dihydrotestosterone (DHT) [2, 5, 17].

The interaction of progestins with sex hormone-binding globulin (SHBG) is also of important consideration. Some progestins may bind SHBG and displace testosterone that is normally bound to SHBG and functionally inactive, allowing more free testosterone to exert androgenic effects [2, 4, 18]. Androgenic progestins, especially those derived from 19-nortestosterone, can decrease the production of SHBG, which translates to increased free testosterone levels, further perpetuating androgenic activity [2].

Natural progesterone is devoid of any androgenic or glucocorticoid activities, although it possesses antimineralocorticoid effects according to some data [11]. Other researchers suggest that natural progesterone exerts antagonist activity at the level of the AR [4, 5]. Natural progesterone is also referred to as P_4 as well as micronized progesterone, and it is molecularly identical to human progesterone [4, 11, 19]. This progestogen has been said to be safer in terms of cardiovascular and breast cancer risks [9, 11] and is the one usually utilized in HRT.

Synthetic progestins may exhibit a range of effects in addition to their progestational action [5, 16], and their properties are summarized in Table 1, although there is discrepancy in the literature regarding the off-target activities of the different progestins. Earlier generation testosterone-derived progestins tend to be more androgenic [7, 8].

Pharmacodynamics of Combined Estrogen and Progestogen Therapies

The interplay of estrogens and progestogens in combined hormonal therapies is complex.

Both estrogen and progestins have antigonadotropic activity by providing negative feedback on the hypothalamic-pituitary axis and thereby decreasing endogenous production of androgens and estrogens [2, 18].

Table 1. FDA-approved synthetic progestins and their properties

Progestin	Gen.	Structural classification	AR activity	Binds SHBG?	Inhibits 5α-reductase?	Other steroid receptor activity	Active metabolites
Desogestrel	3 [5]	Testosterone [5]	n.a. [45]	n.a. [45]			Etonogestrel [45]
Dienogest	4 [16]	Testosterone [5]	– [5, 15]	No [46]	Yes [17]		
Drospirenone	4 [8]	Spironolactone [15]	–– [47]	No [47]		Antimineralocorticoid activity [47]	None [47]
Etonogestrel/ 3-keto-desogestrel	3 [16]	Testosterone [48]	+ [45]/++ [15]	Yes 32% [48]		Weak glucocorticoid activity [15]	Unknown [48]
Levonorgestrel	2 [8]	Testosterone [5]	++ [5, 15]	Yes [49]	Yes [17]		
Medroxyprogesterone acetate	1 [4]	Progesterone [5]	+ [15, 50]	No [50]		Glucocorticoid activity [15]	
Norelgestromin	3 [16]	Testosterone [15]	+ [51]	No [51]			Norgestrel [51]
Norethindrone/ norethisterone	1 [8]	Testosterone [5]	++ [15]	Yes, 36% [52]			
Norethindrone/ norethisterone acetate	1 [8]	Testosterone [5]	n.a. [52]	n.a. [52]			Norethindrone [52]
Norgestimate	3 [16]	Testosterone [5]	+ [53]	n.a. [53]	Yes [17]		Norelgestromin, norgestrel [53]
Norgestrel	2[8]	Testosterone [5]	++ [15]	Yes (highly) [51]			
Segesterone acetate/ nestorone/nesterone	4 [4]	Progesterone [5]	n.a. [15]	No [54]			None [54]

Gen., generation; n.a., not applicable; AR, androgen receptor; ++, androgenic activity; +, weak androgenic activity; –, weak antiandrogenic activity; ––, antiandrogenic activity; SHBG, sex hormone-binding globulin.

The androgenic activity of some progestogens may be counteracted by the concomitant activation of ERs. Ethinyl estradiol/estrogen can increase the levels of SHBG which binds testosterone and therefore limits the amount of free, unbound hormone that is available to exert androgenic effects [2, 7, 18]. Estrogen also inhibits 5α-reductase, decreasing the conversion of testosterone to the more potent DHT [7, 18]. Some authorities assert that regardless of the androgenic properties of the particular progestin, the net effect of all combination oral contraceptives is antiandrogenic when they contain ethinyl estradiol [7, 8]. Some COCs have been FDA-approved for the treatment of acne based on their antiandrogenic effects, and they include: ethinyl estradiol/norgestimate, ethinyl estradiol/norethindrone acetate/ferrous fumarate, ethinyl estradiol/drospirenone and ethinyl estradiol/drospirenone/levomefolate [7, 8].

Bioidentical Hormone Therapy

The American Association of Clinical Endocrinologists advise against the use of bioidentical hormone therapy (BHT), owing to the paucity of high-quality safety and efficacy data as well as the lack of regulation over compounded products [12]. The FDA additionally cautions against claims to the safety, efficacy and superiority of compounded BHTs and their potential to mislead both practitioners and patients [12]. Some noncompounded BHTs have been approved by the FDA for use. The compounded products contain varying levels of estrogen, progesterone and even testosterone based on the provider's discretion and patient's hormonal levels and symptoms. The molecular structures of hormones used in BHTs are unaltered (as opposed to those used in conventional HRTs), which renders them identical to endogenous hormones produced within the body. However, there is no evidence to support that the unaltered molecular structure is more effective or safe. It is thought that the same cardiovascular and malignancy risks apply to BHTs as to other hormonal therapies. BHTs may involve various combinations of estrogens in the form of estradiol, estriol and estrone. The progesterone and testosterone used in compounded BHTs are each only of one form, their naturally found form [20].

Hormones and Hair

Androgens are principal regulators of normal human hair growth [21, 22]. Sebaceous glands, hair follicles and many types of skin cells express AR and the enzyme 5α-reductase, which converts testosterone to its more potent form, DHT [2, 21, 23]. The dermal papilla in the center of the hair bulb is a principal site of androgen action and influences keratinocytes of the hair follicle through paracrine signaling, regulating the size, shape and color of the hair as well as its frequency of regeneration [21, 24–26]. Androgenic or antiandrogenic activity results in loss or growth of scalp hair, respectively [2, 22, 27]. However, follicle response to androgens is variable [2, 25]. Increased levels of DHT can lead to androgenetic alopecia in the scalp but promote a male-type hair growth in other

parts of the body [1, 2]. Additionally, hormones are postulated to play a central role in the progression of the hair cycle; for example, DHT is thought to shorten the anagen phase [28, 29]. The precise mechanisms of hormonal modulation of the hair cycle remain to be elucidated.

Certain polymorphisms of the androgen receptor gene are thought to facilitate ease of activation of the receptor, thus providing a genetic predisposition for androgen-related disorders. These polymorphisms have been demonstrated to be more prevalent in patients with androgenetic alopecia as well as acne and hirsutism [21].

The role of estrogens in hair growth is controversial and complex [6, 20, 24]. The increase in female pattern hair loss (FPHL) following menopause suggests that estrogen promotes hair growth, although high-quality data have not yet become available to confirm an association between hair loss and menopausal status [30]. Studies in ovariectomized mice, serving to model postmenopausal FPHL, have demonstrated that a decrease in estrogen results in hair loss [31]. Estrogen has been postulated to aid hair growth by extending the anagen phase of the hair growth cycle [32], during pregnancy, for example [6]. In the postpartum period, an increase in number of hairs in the telogen phase results in increased hair shedding [5, 6, 24]. Estrogen is presumed to be the principal hormone responsible for changes in hair cycling around pregnancy; however, the interference by other hormones (such as prolactin) cannot be excluded.

The differential expression and function of the two isoforms of ER, ER-α and ER-β, may also be relevant to the effect of estrogen on hair growth. Studies have demonstrated that ER-β is more strongly expressed than ER-α in anagen hair follicles of the nonbalding scalp [33], and FPHL has been linked to polymorphisms of the ER-β gene [6, 34].

In addition to their independent modulation of hair growth, estrogens are thought to treat androgen-dependent disorders by indirectly interfering with androgen action: for example, by increasing SHBG levels and reducing androgen availability [24].

Implications of Hormone Therapies in Hair Loss

Many authors, including those of this review, suggest authors hypothesize that hair loss in addition to acne and hirsutism are side effects attributable to the androgenic effect of progestogens [35, 36]. Additionally, some data have suggested an association between androgenic progestins and alopecia. A postmarketing surveillance study of Norplant, a levonorgestrel (progestin with high androgen activity) implant, noted statistically significant increased rates of alopecia in patients with the implant compared with controls [37]. In another study aiming to assess the incidence of hair loss in women after insertion of a levonorgestrel IUD, the adverse effect of hair loss prompted some women to remove their device; upon removal, some women experienced recovery of their hair loss, which suggests a causal association [38]. This study was met by the severe limitations of reliance on physician reporting of hair loss and inadequate follow-up. In a Finnish study of almost 18,000 women, 15.7% of women with levonorgestrel IUDs reported hair loss [39]. However, authors did not provide details that could support causality, such as timeline of insertion and removal of device, duration and severity of hair loss/growth, and other risk factors for alopecia.

Research thus far has been severely limited and therefore has not yielded high-quality data to establish a causal association between androgenic progestins and hair loss. Additionally, IUDs are intended to release the progestogen locally and minimize systemic absorption; therefore, studies examining the effects of IUDs are likely to underestimate the true impact of androgenic progestins on hair loss.

Few studies have evaluated the efficacy of cyproterone acetate, an antiandrogenic progestin not available in the USA, in the treatment of alopecia in women, with variable results. A year-long randomized trial compared the use of topical minoxidil and cyproterone acetate in 66 women with FPHL and determined that minoxidil was superior in women without hyperandrogenism; however, the subjective improvement in hair loss with cyproterone acetate was equivalent to that of minoxidil in women with other hyperandrogenic symptoms [40]. Another study comparing the effects of flutamide (competitive inhibitor of AR), finasteride (5α-reductase inhibitor) and cyproterone acetate determined that both flutamide and cyproterone acetate resulted in clinical improvement of female hyperandrogenic alopecia compared with untreated controls, but only flutamide yielded statistically significant results [41].

Hormone-Modulating Therapies: SERMs and Aromatase Inhibitors

SERMs are nonsteroidal drugs, originally developed to treat hormone-dependent breast cancer, that can act as estrogen receptor agonists or antagonists depending on the particular tissue and the particular SERM [6, 42]. They also exhibit differential activity with regard to different isoforms of ER [6, 42]. The selective nature of these agents is being exploited to develop new, multifunctional therapies, including those that selectively modulate AR [42], that perhaps may play a future role in the treatment of hair loss. However, there are currently very few data on the implications of SERMs in skin [6]. Aromatase inhibitors, also employed for the treatment of hormone-dependent breast cancer, decrease serum levels of estrogen by preventing its synthesis [6, 43]. SERMs and aromatase inhibitors have been associated with the induction of alopecia with features similar to androgenetic alopecia [6, 43, 44]. It is hypothesized that by inhibiting the activation and signaling of endocrine receptors, these agents cause increased levels of DHT and thus an androgenetic pattern of alopecia [43]. Treatment with topical minoxidil has been associated with clinical improvement in cases of alopecia associated with SERMs/aromatase inhibitors [43].

Conclusion and Authors' Clinical Approach

While the role of androgens is commonly encountered in the study of hair biology, the consequences of commonly prescribed therapies with androgenic properties, as in HRT and COCs, have not been systemically studied, and data are lacking.

Based on the pharmacological properties of these drugs and the current knowledge regarding the pathophysiology of alopecic conditions, we tend to avoid therapies with net androgenic properties in patients with hair loss. Micronized progesterone is the main component of

most HRTs and based on its largely antiandrogenic effect, it is acceptable to be used in women with hair loss. On the other hand, some progestins may be beneficial in treating alopecic disorders based on their antiandrogenic activity and inhibition of 5α-reductase (such as chlormadinone acetate, drospirenone, cyproterone acetate and dienogest). For patients seeking contraception who cannot tolerate the estrogen component in COCs, nonhormonal modalities (such as the copper IUD) or less androgenic progestins (such as the etonogestrel implant) should be considered. We also recommend close work with the gynecologists in order to provide individual tailored, safe and satisfactory hormonal contraception or hormonal replacement.

For breast cancer patients who experience alopecia attributed to SERMs or aromatase inhibitors, the authors' approach is to add topical/oral minoxidil or other nonhormonal modalities to mitigate hair loss while maintaining the endocrine therapy.

In conclusion, there remains the critical need for hormonal therapies to be properly evaluated for effects on hair growth/loss before their implementation in clinical practice.

Key Message

Though data are sparse, commonly prescribed hormone-containing therapies may have important implications for hair loss.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

All authors have contributed to the literature search and composition of paper. All the authors have read and approved the final paper.

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