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Review

Hormonal therapy in female pattern hair loss

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ABSTRACT

Female pattern hair loss is the most common cause of hair loss in women and one of the most common problems seen by dermatologists. This hair loss is a nonscarring alopecia in which loss occurs on the vertex scalp, generally sparing the frontal hairline. Hair loss can have significant psychosocial effects on patients, and treatment can be long and difficult. The influence of hormones on the pathogenesis of female pattern hair loss is not entirely known. The purpose of this paper is to review physiology and potential hormonal mechanisms for the pathogenesis of female pattern hair loss. We also discuss the current hormonal and hormone-modifying therapies that are available to providers as they partner with patients to treat this frustrating issue.

Introduction

Alopecia is a common issue that can cause significant morbidity because even though scalp hair is not biologically essential, it can have great psychological and social significance. The results of a 1993 Glamour magazine survey showed that more than half of women said, "If my hair looks good, I look attractive no matter what I'm wearing or how I look otherwise," and "If my hair isn't right, nothing else can make me feel that I look good" (Cash, 2001). Add to this the fact that more than 21 million women in the United States alone experience female pattern hair loss (FPHL), and it is not surprising that hair loss in women can be a serious cause of psychological stress and morbidity (Pickard-Holley, 1995; van Zuuren et al., 2016). In one study, 55% of affected women displayed symptoms of depression (Camacho and Garcia-Hernandez, 2002). In that same group, 89% of women experienced an improvement of those symptoms after treatment for hair loss (Camacho and Garcia-Hernandez, 2002).

However, the effects of alopecia reach far beyond symptoms of depression and include anxiety, obsessions, dissatisfaction with one's appearance, and low self-esteem (Al-Mutairi and Eldin, 2011; Dlova et al., 2016; Hunt and McHale, 2005; Schmidt et al., 2001). There can be significant disturbance in a patient's social life because they may change their hair style, clothing, or avoid social meetings (Al-Mutairi and Eldin, 2011). One study reported that 40% of surveyed women described marital problems and 63% had career-related issues that they ascribed to their hair loss (Hunt and McHale, 2005). These effects seem to occur regardless of patients' age, race, or degree of hair loss (Dlova et al., 2016; Hunt and McHale, 2005; Schmidt et al., 2001). Another study of more than 200 women found that this psychologic morbidity occurs with equal frequency in women whose hair is typically covered by a headscarf (Erol et al., 2012).

Distress can also come from more than a change in body image. Dlova et al. (2016) found that in a group of black South African women, 52% reported serious worry that others would mistakenly assume that their hair loss was secondary to HIV infection or AIDS. It is critical that clinicians who care for such patients be compassionate and understanding but also have a solid understanding of hair loss so that reasonable expectations can be established and a therapeutic relationship can develop.

FPHL or androgenetic alopecia is the most common cause of hair loss in women and one of the most common chronic problems seen by dermatologists worldwide (Varothai and Bergfeld, 2014). FPHL is a nonscarring form of alopecia in which the frontal hairline is maintained, but there is progressive hair thinning at the vertex of the scalp. Thinning of the hair is secondary to alteration of the hair cycle with shortening of the anagen phase and simultaneous lengthening of telogen. This increase in the resting phase and decrease in the growth phase of the hair cycle results in the miniaturization of hair because long terminal hairs are gradually replaced by short vellus hairs (Messenger and Sinclair, 2006; Sinclair et al., 2011).

Pathophysiology

Despite the name androgenetic alopecia, the exact role of hormones is uncertain. It is well known that androgens affect the growth

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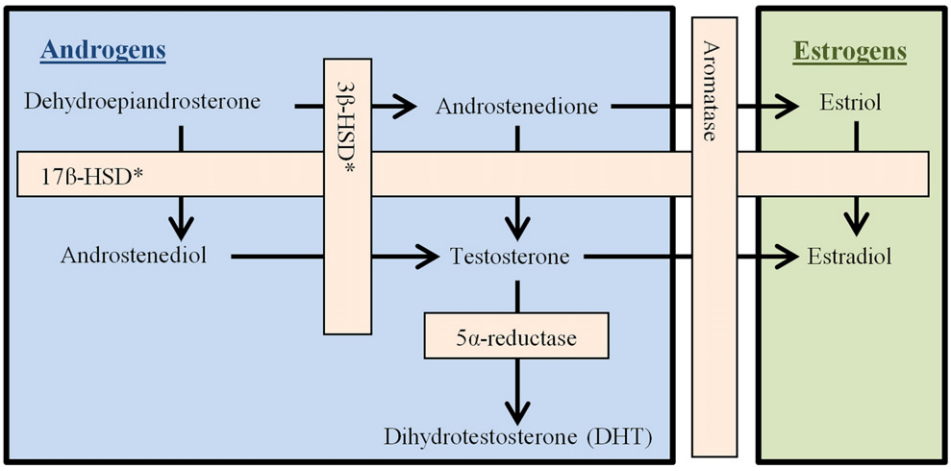

Figure 1. Androgen biosynthesis.

of the scalp and body hair and even Hippocrates observed 2,400 years ago that eunuchs did not experience baldness (Yip et al., 2011). However, hyperandrogenism cannot be the only pathophysiologic mechanism for FPHL because the majority of women with FPHL neither have abnormal androgen levels nor do they demonstrate signs or symptoms of androgen excess (Atanaskova Mesinkovska and Bergfeld, 2013; Schmidt and Shinkai, 2015; Yip et al., 2011). Furthermore, cases have been reported in which FPHL developed in patients with complete androgen insensitivity syndrome or hypopituitarism with no detectable androgen levels (Cousen and Messenger, 2010; Orme et al., 1999).

Male pattern hair loss has been established as androgen-dependent because it is associated with changes in the androgen receptor and responds to antiandrogen therapy (Ellis et al., 2002). With FPHL, genes that encode aromatase, which converts testosterone to estradiol, are also implicated (Yazdabadi et al., 2008; Yip et al., 2009). The process of androgen biosynthesis is depicted in Figure 1.

Androstenedione, which is mostly produced in the ovary and adrenal glands, is converted to testosterone by 17β-hydroxysteroid dehydrogenase. Testosterone then circulates throughout the body to reach its target tissues. Androgen-metabolizing enzymes have been found in many parts of the hair follicle (Table 1; Bolognia et al., 2012). The presence of those enzymes makes the pilosebaceous unit a site of androgen metabolism and synthesis (Fazekas and Sandor, 1973). Circulating free testosterone either binds to intracellular androgen receptors in the hair bulb and dermal papilla, which facilitates miniaturization of the follicle, or is metabolized into dihydrotestosterone (DHT) by the enzyme 5-alpha-reductase. DHT then binds the same receptor but with much greater affinity (Kaufman, 2002; Levy and Emer, 2013). Of the androgens depicted in Figure 1, only DHT and testosterone bind to androgen receptors (Burger, 2002).

Treatment

The process of androgen conversion and subsequent binding to its target receptor are targeted by many hormonal therapies that are currently available including 5-alpha-reductase inhibitors, androgen receptor blockers, and estrogen and oral contraceptive drugs.

5-alpha-reductase inhibitors

It is logical that some reduction in hair loss and miniaturization may occur if the conversion of testosterone to its stronger androgen, DHT, is prevented. The drug class of 5-alpha-reductase inhibitors stops that transition to DHT and leaves androgens that do not bind their receptors as tightly.

Finasteride is a 5-alpha-reductase type II inhibitor, and although it is approved by the U.S. Food and Drug Administration (FDA) for the treatment of male androgenetic alopecia, it is not approved for FPHL. Finasteride is significantly teratogenic and has been shown to cause feminization of male fetuses (Bowman et al., 2003) as well as sexual side effects, depression, headache, nausea, and hot flashes (Varothai and Bergfeld, 2014). The decreased conversion of testosterone to DHT causes a build-up of testosterone, which subsequently converts to estradiol and creates a relative estrogen excess, and this could theoretically increase the risk of breast cancer (Kelly et al., 2016). Studies that use low doses (1 mg daily) showed no significant benefit (Kim et al., 2012; Price et al., 2000). However, one study of 37 premenopausal women who were taking a 2.5-mg dose of finasteride daily with an oral contraceptive pill showed improvement of hair loss in 62% of patients (Iorizzo et al., 2006). Another study of 87 pre- and postmenopausal normoandrogenic patients who were taking a 5-mg dose of finasteride per day for 12 months showed a significant increase in both hair density and thickness (Yeon et al., 2011). The effectiveness of finasteride does not seem to differ between pre- and postmenopausal patients (Yeon et al., 2011). Finasteride is classified as pregnancy category X.

Dutasteride is a 5-alpha-reductase inhibitor that binds both types I and II enzymes. Compared with finasteride, its inhibition of type II enzymes is three times more potent; its inhibition of type I enzymes is 100 times more potent (Clark et al., 2004). Dutasteride is not approved for the treatment of FPHL by the FDA, and ongoing studies on the efficacy of the inhibitor are promising but largely focus on male patients (Gupta and Charrette, 2014; Olsen et al., 2006). A study of women after 3 years of therapy showed that dutasteride may be more effective than finasteride in women under 50 years of age as measured by hair thickness (not hair density) at the center and vertex scalp (Boersma et al., 2014). One case report of a 46-

Table 1
Androgen-metabolizing enzymes in the pilosebaceous unit

Dermal Papilla	Aromatase, 17β-HSD, 5α-reductase (type II)
Outer Root Sheath	Aromatase, 17β-HSD, 5α-reductase (types I & II)
Inner Root Sheath	Aromatase, 5α-reductase (types I & II)
Sebaceous Gland	Aromatase, 5α-reductase (type I)
Sebaceous Duct	5α-reductase (type II)

17β-HSD, 17β-hydroxysteroid dehydrogenase.