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Evaluation of the role of topical estradiol in treating female pattern hair loss: what do we know till now?

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Abstract:Background: Female pattern hair loss (FPHL) is the most prevalent form of hair loss among women. A lot of drugs and interventions were tried but minoxidil is still the only FDA approved topical therapy. Hormonal therapy in the form of topical estradiolis commonly used in Europe and South Korea. The aim of our study is to evaluate the role of topical estradiol in treating FPHl in previous studies. **Methods:**A thorough literature search of topical estradiol in treating female androgenic alopecia using PubMed was conducted, and all references related to hair loss were reviewed.

This study was conducted at the department of Dermatology and Andrology, Helwan University from 2022 till 2023.**Results:** Few clinical trials were conducted using topical estradiol either alone or in combination with topical minoxidil. Topical estradiol showed efficacy in stabilization of hair loss, increasing hair density and thickness in some clinical trials. **Conclusion:** More studies are needed to evaluate if adding topical estradiol to minoxidil in treating FPHL is more effective and to evaluate its safety.

Keywords:*FPHL, Topical Estradiol, Minoxidil, AGA, Hair loss, Androgenic Alopecia.*

Introduction

Androgenic alopecia (AGA) is an old term that has been used to describe male and female pattern hair loss [1].

However, female pattern hair loss (FPHL) is now a more accepted term in women with AGA as the role of androgens in its patho physiology is still unsettled [2][3].

FPHL is one of the most common conditions among women seeking dermatological consultations. and one of the most challenging dermatological conditions [4][5]. Studies reported that 55% of women suffering from FPHL experienced symptoms of depression, 40% experienced marital problems, 64% had career difficulties and 70% had a negative body image and poorer self-esteem [6][7][8].

The main dermoscopic feature of FPHL is increased ratio of vellus hairs to terminal hairs resulting in progressive miniaturization of the hair follicles which follows a characteristic pattern of distribution [9].

There are multiple factors that contribute to FPHL pathogenesis including genetic, hormonal, inflammatory and environmental factors [10].

Epidemiology:

FPHL has two incidence peaks, the first is during reproductive years (early onset) and the second is after menopause (late onset) [2].

The incidence of FPHL increases with age reaching 55% in women over 70 years of age. Severe forms of hair loss are rarely seen during puberty. The two peaks outweigh that there is a
hormonal role in the onset of FPHL. Women in all populations are affected by FPHL with higher prevalence in Caucasian women [4][11].

Pathophysiology:

- **Role of Genetic factor:**

50% of women with FPHL have a family history of female hair loss, so it is thought that there is a genetic component related to the disease [11].

Genetic pre-disposition is always present and FPHL is now well established to have a polygenic mode of inheritance. The genetic factor determines the pattern, progression, age of onset, and severity of the condition [12].

The estrogen receptor-polymorphisms has been identified to have a role in FPHL development [13].

Role of androgens:

In men, there's a clear association between androgens and male AGA, specifically dihydrotestosterone (DHT) which binds to androgen receptors on susceptible hair follicles [14].

Androgens were thought to be responsible for FPHL, because women with hyperandrogenic conditions like polycystic ovarian syndrome experience early-onset FPHL. However, the majority of the affected women have normal androgen levels which means that androgens are not involved [15][16]. Moreover, FPHL may develop even in absence of androgens [17].

Dihydrotestosterone (DHT) is the end product of testosterone metabolism by 5α reductase enzyme. DHT is more potent than testosterone and of higher affinity to androgen receptors. It is also considered the main androgen mediator in the scalp. Androgens also impair stem cell differentiation in hair follicles through disregulation of WNT signaling pathway which is required for anagen initiation [18].

It was observed that Aromatase inhibitor medications that cause decreased estrogen levels induce hair loss, and topical estrogens have been used widely as hair growth stimulants in FPHL [19].

CLINICAL FEATURES

FPHL usually begins with slowly progressive hair thinning [20].and it may be associated with increased hair shedding. The vertex, upper parietal scalp are the most affected areas. The frontal hair line is always preserved unlike in men where there is frontal hair line recession in most cases.

DIAGNOSIS:

Diagnosis is usually made clinically. Trichoscopy is used to confirm the diagnosis especially in early cases or to differentiate FPHL from other hair loss disorders[21].

dermoscope [22].

The main trichoscopic findings seen in FPHL are diversity of hair shaft diameter, brown peripilar sign, white peripilar sign, pinpoint white dots, yellow dots, and scalp honeycomb pigmentation. All the trichoscopic abnormalities are more prominent in the crown area compared with the occipital area [23][24].

Major and minor criteria were suggested for diagnosis of FPHL by ***Rakowska et al., 2009.***

Major criteria include increased frontal to occipital ratio of:

- More than four yellow dots in four images with 70-fold magnification in the frontal area.
- More than 10% of thin hair (<0.03 mm) in the frontal area.
- Decreased hair thickness in the frontal area compared to the occipital area.

Minor criteria include increased frontal to occipital ratio of:

- Single-hair pilosebaceous units
- Vellus hairs
- Perifollicular discoloration.

Fulfillment of two major criteria or one major and two minor criteria allows the diagnosis of FPHL [25].

Treatment:

Treatment of FPHL aims mainly to promote hair regrowth and arrest the disease progression. The first-line treatment for FPHL is topical minoxidil, treatment of hyperandrogenism or any nutritional deficiencies if present are needed. Oral anti-androgens like cyproterone acetate and spironolactone can be used. Hair transplantation may be considered in severe selected cases [26][27].

Topical Minoxidil and Topical Estradiol in treating FPHL:

Topical minoxidil*:*

In the 1970s, oral minoxidil was tried firstly as a potent peripheral vasodilator for treatment of severe hypertension. Serious side effects were observed so oral minoxidil was reserved for severe cases of resistant hypertension after failure of the maximum dose of three antihypertensive drugs. Hypertrichosis was observed in about 20% of patients who used oral minoxidil and this give the idea of the development of topical minoxidil in 1987 for the treatment of androgenic alopecia for males first and then it wasapproved for females [28][29][30][31].Topical minoxidil is the only FDA approved topical therapy for FPHL while topical minoxidil and oral finasteride are approved only in male AGA. Although, topical minoxidil has significant results, it also has some obstacles like financial cost, long treatment duration, compliance, limited absorption and contact dermatitis [32].

Minoxidil is generally used for hair loss in patients who are over 18 years. However, it is used also in children and considered off-label use in cases of alopecia areata, hair shaft disorders, AGA in children and short anagen syndrome. Long-term use of minoxidil is necessary to maintain the results, as drug discontinuation causes regression of these results [33][34][35].

Mechanism of action:

The mechanism of action of minoxidil on hair follicles is still not clear. Minoxidil is a piperidino-pyrimidine derivative. It is a prodrug which is converted to its active metabolite minoxidil sulfate to exert its pharmacological actions. Different individuals have variable sulfotransferase enzymatic activity leading to variable response to topical minoxidil[36]. Minoxidil sulfate is responsible for the vascular and the follicular actions of minoxidil [37]. It has an antihypertensive effect through opening the plasma membrane adenosine triphosphate (ATP)-sensitive potassium channels (KATP channels) [37].

The exact mechanism by which minoxidil enhances hair growth is still not completely understood. It has been suggested that minoxidil promotes hair growth through increasing local blood flow [38][32].

Oral minoxidil:

Low dose oral minoxidil is a new therapy for treatment of hair loss especially AGA but it's still not approved by the FDA. It showed efficacy and tolerability with doses varying from 0.25 to 5 mg daily. In FPHL, lower

doses are favorable. Low dose oral minoxidil also showed a good safety profile and few contraindications making it a good option for healthy individuals who have problems with the topical form [39][40].

Adverse Effects:

Minoxidil is well tolerated in most cases; but some side effects were noticed in some patients, including Allergic contact dermatitis which is the most common side effect. It is caused mainly by minoxidil and propylene glycol. In this case, minoxidil foam is a good option. Minoxidil also causes minoxidil-induced telogen effluvium manifested by marked shedding in the beginning of treatment due to shortening of the telogen phase. Scalp irritation, redness, scales and pruritus also occur. Minoxidil also causes hypertrichosis which can be localized or generalized and occurs with both topical and oral forms but more common with the oral form and with 5% versus 2% minoxidil. Some studies suggested that this side effect is due to prolongation of the anagen phase [37][32].

Oral minoxidil is also associated with significant adverse effects like:

- Rare but severe reactions include pericarditis, pericardial effusion, cardiac tamponade, exacerbating congestive heart failure, and worsening angina.
- Oral minoxidil administration can lead to significant hypotension. Hypertrichosis, edema, tachycardia, and weight gain are also caused by oral minoxidil [41]. **Non-responding cases:**

The response to topical minoxidil treatment can be predicted by enzymatic assay of sulfotransferase enzyme activity in plucked hair follicles which showed very high accuracy by detecting about 94% of the non-responders to topical minoxidil [36][42].

McCoy et al., 2016, demonstrated that increasing topical minoxidil concentration up to 15% in cases predicted to be non-responders enhanced the clinical response in comparison to the classic 5% minoxidil [43].

Minoxidil sulfate-based solution (MXS) is a novel formula that has been used increasingly as minoxidil sulfate is the active metabolite of minoxidil and this novel formula showed promising effect in cases with low sulfotransferase activity [44][45].

Topical estradiol:

Estradiol is a steroid sex hormone produced mainly by the ovaries in the human body. There are four estrogen forms: estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4). Estradiol is the most potent estrogen and the predominant estrogen during reproductive years. It plays an important role in regulating the menstrual cycle. It also affects the cardiovascular, neurologic, skeletal and vascular systems [46][47].

Estrogen plays a major role in maintenance of human skin. It enhances collagen quality and amount, skin thickness and vascularization. This is supported by the postmenopausal skin changes that occur in women[48].

During menopause, estrogen significantly decreases as a result of decreased ovarian function, and this results in development of the unpleasant postmenopausal symptoms like vaginal dryness, hot flushes and dyspareunia. Estradiol can be synthesized by extragonadal sites after menopause like adipose tissue, brain, and bone. During reproductive period, estradiol plays a protective role against cardiovascular diseases through regulation of cholesterol and triglyceride metabolism [49][50].

Therapeutic forms:

Estradiol can be administered via multiple routes including oral forms, topical creams, solutions and patches and intramuscular route [51].

Sustained-release estradiol vaginal rings were also used[52].

Mechanism of Action:

Inside the granulosa cells of the ovary, estrone is converted to estradiol by 17-beta-hydroxysteroid dehydrogenase enzyme. It is also produced through testosterone aromatization by aromatase enzyme. Estradiol diffuses simply across the plasma cell membrane, binds to its intracellular nuclear receptors and regulates DNA transcription in various tissues including skin [47].

Estrogen Receptors in hair follicles:

The estrogen receptors (ER), ERα and ERβ are one of the nuclear receptors located in the nucleus of target cells [53][54].

Estrogen receptors are widely represented in hair follicles, especially ERβ which is expressed in dermal papilla cells, outer root sheath, connective tissue sheath and epithelial matrix cells suggesting that estrogen targets those cells and has a significant role in regulation of hair follicle growth cycle. It was also found that ERβ other than ERα is expressed in the bulge region cells of the outer root sheath which are considered the stem cells of the keratinocytes of the hair follicle and epidermis [55][56][57].

The biopsies taken from women and men with androgenetic alopecia showed that aromatase levels were higher in hair follicles of the occipital scalp compared to that in the frontal scalp. The same study showed that aromatase levels in the hair follicles of the frontal area of scalp in women were six times higher than those in males[58][59].

Results of previous studies on topical estradiol for treating FPHL:

Topical estradiol solutions have been widely used especially in Europe and South America for treatment of FPHL [60][61].

Some clinical trials were done on the usage of low doses of topical estradiol solution for treatment of FPHL and it showed its safety[62][63][64].

In a previous placebo-controlled study on 51 patients with FPHL who received 0.025 % topical alpha estradiol for 6 months and evaluated by trichogram, 63% of patients had reduced amount of telogen hairs in contrast to 37% of cases in the control group. Additionally, 11% of the patients in the estradiol group worsened, in contrast to 50% in the control group. There was no increase in hair counts in both groups [62].

Similar results were also reported by ***Georgala et al., 2004***, where 30 % of cases showed improvement in anagen to telogen ratio after application of 0.03 % topical estradiol valerate solution for 6 months in comparison to placebo [65]. This was revisited again by ***Kim et al., 2012,*** where they evaluated the efficacy and safety of the commercial EllCranell® topical 0.025% alpha estradiol solution on 53 Korean women with FPHL. Another study was conducted to evaluate efficacy of topical 0.025% 17α-estradiol and 3% minoxidil solutions on 34 Korean women with FPHL after 6 months of treatment. Evaluation was done by phototrichogram, and the majority of their patients exhibited significant increase in hair count and hair thickness [64].

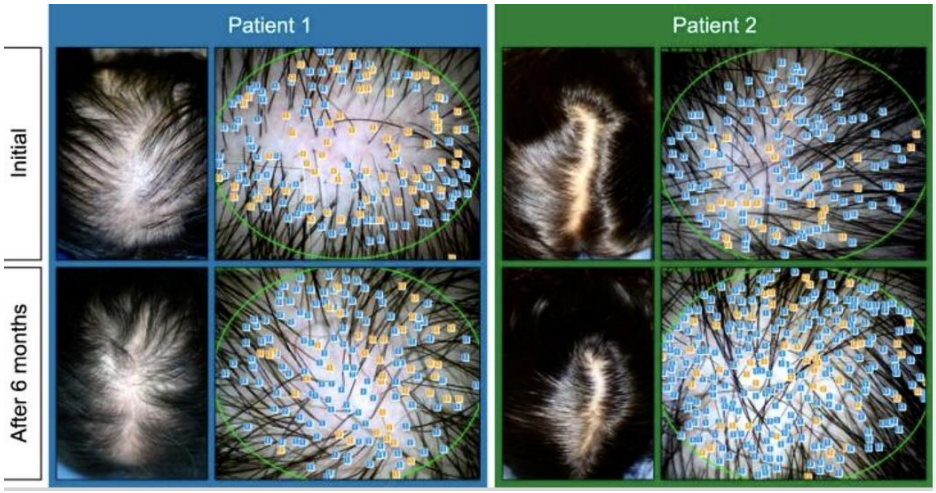
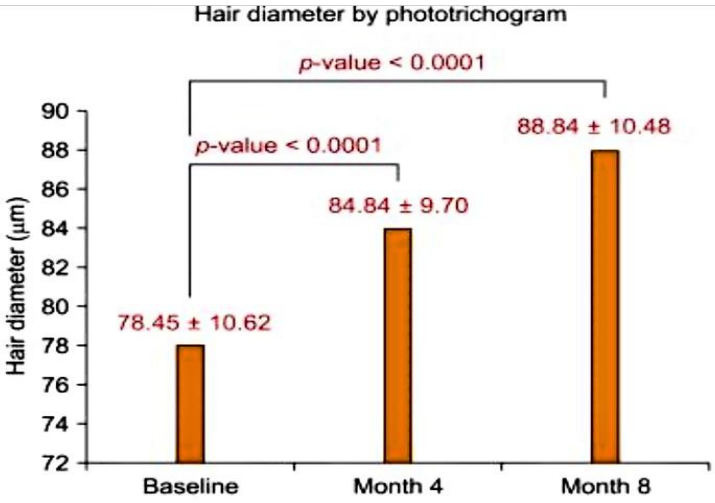


Figure 1 showing 2 patients after 6 months of treatment with topical estradiol and minoxidil in a study conducted by **Choe et al., 2017.**



	n	Mean±SD	Median	Min, max	95% CI	*p*-value
Baseline (µm)	**51**	78.45 ± 10.62	**78**	56, 108		
Month 4 (µm)	**51**	84.84 ± 9.70	**84**	69, 117		
Month 8 (µm)	**51**	88.84 ± 10.48	**88**	68, 116		
Difference 1	**51**	6.39 ± 8.21	**7**	−12, 25	**6.39 [4.08, 8.70]**	**< 0.0001**
Difference 2	**51**	10.39 ± 10.08	**12**	−11, 41	**10.39 [7.56, 13.23]**	**< 0.0001**

Table (1) showing efficacy of 4 months treatment with topical estradiol on hair diameter in patients with FPHL in a study conducted by **Kim et al., 2012.**

None of the aforementioned studies reported major adverse events except the study conducted by ***Georgala et al., 2004***, that reported post-menopausal bleeding in 2 women after 17 and 22 weeks of treatment, and one patient developed breast cancer several months after completion of the treatment [65].

Side Effects:

The most reported side effects with the topical forms are mild erythema, headache, breast tenderness, pruritus, local irritation, endometrial thickening, vaginal bleeding and vaginal moniliasis [66][67].

Contraindications:

Estradiol is contraindicated in women with increased risk of breast cancer or endometrial cancer [68]. It is also contraindicated during pregnancy and in cases with allergy or angioedema reaction to estradiol or any of its components, cases with abnormal genital bleeding, cardiovascular disorders, coagulation disorders, protein S and C deficiency [52].

Safety of topical estradiol:

Nowadays, there are various transdermal estradiol preparations that are FDA approved for treatment of postmenopausal symptoms including gel, cream, spray, vaginal rings and patches [69].

Low-dose estrogen is considered to be 0.3mg or less of conjugated estrogen, 0.5mg or less of oral micronized estradiol, 2.5µg or less of oral ethinyl estradiol, or 25µg or less of transdermal estradiol. Low-doses of estrogen formulations are more favorable and considered safer than high-dose forms in terms of venous thromboembolic events, cardiovascular symptoms, stroke, and breast cancer., They also decrease the unacceptable adverse effects like irregular bleeding and breast tenderness [70][71].

A systematic review was carried out in 2019 to evaluate endometrial hyperplasia or cancer incidence with unopposed trans-vaginal estrogens of various doses and durations. Of 5,593 abstracts identified from the literature search and 47 studies from other sources, 36 articles and 2 abstracts were eligible, describing 20 randomized controlled studies, 8 interventional studies, and 10 observational studies. The eligible studies

had to report menopausal vaginal estrogen use and endometrial histology, or incidence of endometrial hyperplasia or cancer.

Clinical evidence from this systematic review did not support an increased risk of endometrial hyperplasia or cancer with with low doses of vaginal estrogens. Rates of endometrial cancer and hyperplasia were 0.03% and 0.4%, respectively, from 20 RCTs (2,983 women). Reports of endometrial hyperplasia were observed with various doses and durations and appeared sporadic and consistent with endometrial hyperplasia rates in the general population except 1.25 mg conjugated equine estrogens used 21 days on/7 days off, which appeared to be associated with an increased risk of endometrial hyperplasia (2 cases of 28 women) [72].
Another systematic review included various clinical trials and observational studies to evaluate the efficacy and safety of topical estrogenin different forms (gel, patch and cream) variable doses (from 0.01micro gram up to 2.5 mg), different application sites (vaginal, arms, face, legs). In some studies evaluation was done by serum E2, FSH, prolactin.
Side effects were rarely reported and if presented, were very minimal like mild erythema, transient breast tenderness. Most of the studies reported no systemic side effects like vasomotor symptoms, vaginal bleeding or edema [73].

Conclusion: FPHL is a very challenging condition. Many drugs have been tried to control the disease and enhance hair regrowth. The efficacy of minoxidil was proven in many studies and it's the only FDA approved topical therapy. Topical estradiol was tried in few clinical trials, and it showed efficacy in some of them.
More clinical trials are needed to determine if adding topical estradiol to topical minoxidil in the management plan of FPHL is more effective and worthy especially with the concerns related to using hormonal therapy and the fear of increasing the risk of breast cancer and vaginal bleeding.

Conflicts of interest: No conflicts of interest were present

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