ISSN Print: 2664-6471
ISSN Online: 2664-648X
Impact Factor: RJIF 5.42
IJDR 2024; 6(1): 32-39
www.dermatologyjournal.in
Received: 09-08-2024
Accepted: 15-09-2024

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Effectiveness of combined topical ethinylestradiol and minoxidil versus minoxidil alone in treating female pattern hair loss

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DOI: https://doi.org/10.33545/26646471.2024.v6.i1a.46

Abstract
Background: Trichoscopy is an effective tool in establishing the diagnosis of female pattern hair loss and a scalp biopsy is seldom needed to validate the diagnosis.
Aim: We sought to determine effectiveness and safety of combination therapy of topical ethinylestradiol 0.01% and minoxidil 2% versus topical minoxidil 2% alone in female pattern hair loss therapy.
Methods: This randomized comparative clinical trial is a clinical trial carried out on 43 female patients, aged from 18 to 55 years, suffered from female pattern hair loss of Ludwig grade I-II-III. Patients who met the criteria were split into two groups at random using the closed-envelop technique: Group A (EMX) included 22 participants who put a topical solution of minoxidil 2% mixed with ethinylestradiol 0.01% for 24 weeks. Group B (MX) included 21 participants who applied topical minoxidil 2% solution only for 24 weeks.
Results: At end of study period, there was no significant correlation between trichoscopic changes and disease duration in both groups. Relation between changes in frontal region and disease disease severity within EMX group was no statistical significance in both groups.
Conclusions: Both study preparations (ethinylestradiol 0.01% mixed with minoxidil 2% and minoxidil 2% alone) were almost equally effective in enhancement of hair growth in female pattern hair loss with superiority of the minoxidil only preparation regarding tolerability with less side effects during the treatment duration.

Keywords: Ethinylestradiol, minoxidil, hair loss, trichoscopy

Introduction

Female pattern hair loss (FPHL) is one of the most prevalent forms of hair loss. It is distinguished by the gradual transformation of terminal hairs into vellus hairs due to the continuous shrinkage of the hair follicles and the shortening of the anagen phase [1].

It varies in severity, age of onset and pattern of distribution of hair loss. The pathogenesis of androgenic alopecia (AGA) depends on the interaction of endocrine factors and genetic predisposition [2]. Clinical examination is typically used to make the diagnosis. Trichoscopy, which is the dermoscopic imaging of the scalp and hair, confirms the diagnosis [3] and in rare cases, a biopsy would be necessary to distinguish androgenetic alopecia from alopecia incognita or chronic telogen effluvium [4].

The primary trichoscopic observations of AGA are the peripilar sign (PPS), the preponderance of single hair pilosebaceous units, the diversity of hair shaft diameters with an increased number of miniaturised vellus hairs, particularly in the fronto-parietal region, and the yellow spots [5]. Different therapeutic and surgical techniques are currently used for management of FPHL, but few medications have a proven effect [6].

Minoxidil is the only FDA approved topical therapy for FPHL. Although it has significant results, it also has some drawbacks like long treatment duration, scalp irritation and compliance [7].

Minoxidil is a piperidinopyrimidine derivative and its mechanism of action is still not entirely clear, it causes potent peripheral vasodilatation via opening the potassium channels leading to nitric oxide release, this results in prolongation of anagen phase and shortening of telogen phase of hair follicles [8].

In addition to minoxidil, 17α-estradiol which is an analogue of the female hormone 17β-estradiol has been used commonly in Korea, Europe and South America for treatment of FPHL [9]. Estradiol reduces the conversion of testosterone to dihydrotestosterone (DHT) by either directly inhibiting 5 α-reductase or indirectly converting testosterone into less potent steroids [10].

There are many benefits to spray-on medicine delivery over traditional methods. It is primarily a noninvasive medication administration technique that offers quick drying, adjustable dosage, and a lower chance of drug loss or transfer. Spray-on cosmetics have been effectively applied to the skin for both topical and local indications. The FDA approved an estradiol spray in 2007 under the name Evamist, which was one of the first spray-on systems for systemic use [11].

By delivering the medication into the stratum corneum, the spray-on technique creates a depot or reservoir for the drug's future penetration into deeper layers of the skin. It is thought that the excess medication deposited on the skin's surface keeps the stratum corneum's drug saturation levels stable [12].

Combination therapies with different mechanisms of action are widely utilized in various medical fields to achieve a greater effect than using a single drug [13]. Accordingly, the aim of our present randomized comparative clinical trial was to contrast effectiveness and safety of combination therapy of topical minoxidil 2% solution mixed with ethinylestradiol 0.01% (EMX) solution to minoxidil 2% solution (MX) on FPHL.

We sought to assess the effectiveness and safety of combination therapy of topical ethinylestradiol 0.01% and minoxidil 2% versus topical minoxidil 2% alone in FPHL therapy.

Material and Methods

This randomized comparative clinical trial is a clinical trial carried out on 43 female patients, aged from 18 to 55 years, suffered from FPHL of Ludwig grade I-II-III. The Ethical Scientific Committee of the Dermatology and Andrology Department of Ahmed Maher Hospital, Egypt. Before the study began, they were all given an explanation of its purpose and asked to sign a written informed consent form.

Exclusion criteria were pregnant or lactating females. Other than FPHL, any concurrent or prior hair problem. Dehydroepiandrosterone sulphate (DHEAS) and serum testosterone levels that are abnormal (free and total). Those receiving hormone replacement treatment or other drugs that impair hair growth. patients having a history of deep vein thrombosis, liver, kidney, or breast cancer, or any other illness that is thought to be incompatible with taking any of the study medications. Medical disorders that result in hair loss, such as autoimmune diseases. History of allergic reactions to any of the solutions' ingredients.

Randomization

Patients who met the criteria were split into two groups at random using the closed-envelop technique: Group A (EMX) included 22 participants who put a topical solution of minoxidil 2% mixed with ethinylestradiol 0.01% for 24 weeks. Group B (MX) included 21 participants who applied topical minoxidil 2% solution only for 24 weeks.

All patients were subjected to history taking, testing for serum level DHEAS and serum testosterone (free and total) before treatment to exclude hormonal abnormalities, FPHL diagnosis [There are more thin and vellus hairs (more than 10%), follicular units with one or two hairs rather than the predominance of follicular units with three or more hairs, and hair shaft thickness heterogeneity (More than 20% of observed hair shafts are thinner than terminal hair shafts) in the frontal area as opposed to the occipital area] and dermoscopic photo-trichogram and clinical photographs [at baseline and repeated at week 16 and week 24].

Every patient received a single, unlabeled spray bottle with at least 60 ml of test drug, which had to be filled every 4 weeks. The patients were blinded as to which type of medication they used. In order to promote absorption, subjects were told to apply the medication twice a day using a pre-dosed applicator and massage their scalps for one minute. Throughout the study, they were instructed to keep their hair in the same color, length, and style. At the conclusion of the therapy period, patients were asked to use a 4-point rating system to indicate how satisfied they were (0 = not satisfied, 1 = slightly satisfied, 2 = moderately satisfied, 3 = greatly satisfied) through a self-administrated questionnaire [14].

Trichoscopy

Fotofinder II's overview mode was used to take pictures of the volunteers in both frontal and occipital views (Germany, model: Medicam 1000, version 2.0.41.18-(x64)). It enables 20–150 times magnification for scalp visibility. The two areas were marked as follows:

Frontal area [F]: a place where the line from the tip of the snout to the line joining the two tips of the ears crossed. Occipital [O]: an external occipital protuberance point.

In order to get high-quality magnification of 1 cm2 of scalp region to the size of the computer screen, images were captured at 20 and 50 times magnification. In an area of roughly 1 cm2, the dermoscopic features of the two locations were examined using the fotofinder's trichoscale analysis system (090.3cm2). A comparison of baseline and 24 weeks measurements was made to assess the difference between the two groups' average number of hairs per follicular unit, hair density, and hair thickness.

Clinical photographic

At baseline, week 16, and week 24, clinical photos of the frontal and vertex views were taken with the hair parted in the middle and combed out from the centre. The photos were edited to maintain a consistent exposure, lighting, and camera perspective. Two dermatologists who were blind to the treatment group assessed paired (baseline and week 24) photos, and an average was determined using a 7-point scoring system (-3 = marked deterioration, -2 = moderate deterioration, -1 = mild deterioration, 0 = no change, 1 = mild improvement, 2 = moderate improvement, 3 = marked improvement.

Minoxidil/Ethinyl estradiol spray-on drug preparation:

In our study, a spray-on system comprising minoxidil and/or ethinyl estradiol is presented. The spray-on system is made up of an aqueous solvent mixture that contains 4% (w/v) citric acid, 30% (v/v) propylene glycol, and 30% (v/v) polyethylene glycol 400. Utilizing a magnetic stirrer set at 500 rpm, a precisely weighed quantity of minoxidil and/or ethinyl estradiol were dissolved in the solvent combination.

Statistical analysis: SPSS v28 (IBM Inc., Armonk, NY, USA) was employed to conduct the statistical analysis. The

mean and standard deviation (SD) of quantitative variables were presented and contrasted among the two groups utilizing an unpaired Student's t-test. Chi-square test or Fisher's exact test was employed to analyze qualitative variables, which were displayed as frequency and percentage (%) when appropriate. Wilcoxon signed rank test used for comparison numerical variables for variables paired (matched) samples. Several variables were correlated utilizing Spearman rank correlation equation. Statistically significant two-sided p values were those that were < 0.05. P values below 0.01 were regarded as statistically significant. It was deemed statistically significant when the P value was < 0.001.

Results

There was no difference of statistical significance between the two groups as regards age, disease duration or disease severity. Table 1

All recruits had improved hair density, hair thickness and average number of hair (s) per unit by 28.95±17.78%, 6.23 ±12.03% and 13.98± 14.8% in the frontal area, and by 14.3±18.98%, 7.1±10% and 7.55±13.26% respectively in the occipital area. Table 2

At the baseline, both groups' frontal and occipital hair densities, thicknesses, and numbers of hairs per unit follicle were comparable. There was no statistical significance in hair density, hair thickness and number of hair(s)/follicular unit between both groups at baseline. There was no statistically significant variation in hair thickness and hair density between both groups at end of treatment period. Table 3

There was as an intragroup statistically significant increase in the mean frontal and occipital hair thickness, hair(s) /follicular unit within EMX group at end of treatment period. No statistically significant difference was existed in hair density between both groups at the end of treatment period (p = 0.75 for frontal and 0.80 for occipital). The absolute change in hair(s) /follicular unit, hair thickness and hair density in EMX group did not statistically differ from that of MX group neither in the frontal nor the occipital region. Although all trichoscopic parameters showed better absolute improvement within the EMX group than MX group, this difference was not statistically significant. Table 4

The percentile changes in hair density, hair thickness and hair(s) /follicular unit in EMX group did not statistically differ from that of MX group neither in the frontal nor the occipital region. In EMX group there was a significant difference in the baseline hair density, thickness and average number of hairs per unit between frontal and occipital regions (p=0.001, 0.00 and 0.00 respectively). In the MX group, there was a significant difference in the baseline hair density, thickness and average number of hair(s) per unit between frontal and occipital regions (P=0.00, 0.01 and 0.00 respectively). Table 5

At the end of treatment period, there was no significant difference in the absolute mean increase in hair density, hair thickness and hair(s)/ follicular unit between frontal and occipital regions (p =0.067, 0.411 & 0.240 respectively). There was a significant difference in the absolute mean rise in hair density between frontal and occipital regions (p =0.01), but not for hair thickness and hair(s) /follicular unit (p =0.14 & 0.268 respectively). There was a significant difference in the percentage rise in hair density between frontal and occipital regions (p =0.033), but not for hair thickness and hair(s)/ follicular unit. The improvement was better in the frontal area in both EMX and MX groups in comparison to the occipital area except for absolute and percent change in hair thickness in MX group which was better for the occipital area. Table 6

Clinical photographic evaluation at the end of the research by blinded dermatologists was no statistically significant difference between the 2 groups. Satisfaction was larger among EMX group patients, and this was statistically significant (p =0.023). Reported side effects in both groups during the study were shown at Table 7

At end of study period, there was no significant correlation between trichoscopic changes and disease duration in both groups. Table 8

Relation between changes in frontal region and disease disease severity within EMX group was no statistical significance in both groups. Table 9

Table 1: Demographic and clinical data of the study group

		EMX N=22	MX N=21	p- value
Age (years)		30.36±7.86	32.29-10.44	0.593
Duration		4.5±2.36	5.67-4.07	0.566
Severity	Mild (Ludwig scale I) n (%)	8(36.4%)	12(57.2%)	0.362
	Moderate (Ludwig scale II) n (%)	9(40.9%)	5(23.8%)	
	Severe (Ludwig scale III) n (%)	5(22.7%)	4(19%)	

Data are presented as mean SD or number (%).

Table 2: Trichoscopic features of all patients at baseline and at end of study period

		Frontal		Occipital	
		Baseline N=40	Final N=40	Baseline N=40	Final N=40
Hair Density (hair/cm²)	Mean	135.42	172.8	160	179.28
	SD	27.63	36.56	27.85	29.11
	p value	<0.0001*		<0.0001*	
Hair thickness (μm)	Mean	50.21	53	54.3	57.57
	SD	7.87	9.18	7.29	8.87
	p value	0.004*		<0.001*	
Hair(s)/foll. Unit	Mean	1.71	1.94	2.17	2.34
	SD	0.18	0.27	0.3	0.29
	p value	<0.001*		0.002*	

*: Significant, p value< 0.05

Table 3: Trichoscopic features of studied groups at baseline and after 24 weeks

		Hair Density (hair/cm²)		Hair Thickness)µm(		Hair / fol. Unit	
		EMX	MX	EMX	MX	EMX	MX
Baseline	Frontal	132.68 ±27.4	138.29 ±28.22	48.50±7.99	52±7.58	1.7±0.2	1.72±0.16
	P value	0.3		0.19		0.618	
	Occipital	153.27±24.38	167.4±30.03	53.77±7.19	54.9±7.52	2.14 ±0.28	2.21±0.34
	P value	0.15		0.50		0.61	
Final	Frontal	175.55±35.9	170.05±37	52.15±9.68	53.85±8.82	1.96±0.26	1.93±0.28
	P value	0.75		0.50		0.96	
	Occipital	182±31	176.55±27	56.25±8.25	58.9±9.47	2.34±0.3	2.34±0.28
	P value	0.8		0.43		0.86	

Data are presented as mean SD or number (%).

Table 4: Trichoscopic features and absolute changes in Trichoscopic features of studied groups at end of treatment period

		EMX				MX			
		Frontal		Occipital		Frontal		Occipital	
		Baseline	Final	Baseline	Final	Baseline	Final	Baseline	Final
Hair Density (hair/cm²)	Mean	132.68	175.55	153.27	182	138.29	170.05	167.14	176.55
	SD	27.44	35.92	24.38	31	28.224	37.92	30.035	27.626
	p value	0.00*		0.00*		0.00*		0.01*	
Hair Thickness (µm)	Mean	48.50	52.15	53.77	56.25	52	53.85	54.9	58.90
	SD	7.93	9.68	7.19	8.258	7.589	8.827	7.523	9.475
	p value	0.010*		0.011*		0.198		0.001*	
Hair(s)/ fol. unit	Mean	1.70	1.96	2.14	2.346	1.726	1.935	2.212	2.348
	SD	0.207	0.260	0.281	0.305	0.161	0.289	0.34	0.283
	p value	0.001*		0.033*		0.004*		0.033*	
Hair Density (hair/cm²)	Mean	+43		+32.5		+27.95		+12.80	
	SD	21.036		21.807		29.237		18.828	
	p value	0.120				0.176			
Hair thickness (µm)	Mean	+4.2		+1.60		+3.05		+4.40	
	SD	6.153		5.605		4.915		5.529	
	p value	0.116				0.847			
Hair(s)/ foll. Unit	Mean	+0.253				+0.212			
	SD	0.254				0.240			
	p value	0.636							

*: Significant, p value< 0.05.

Table 5: Percentile changes in Trichoscopic features at end of study period and comparison between baseline trichoscopic features at baseline between frontal and occipital region within EMX and MX groups

		Frontal		Occipital	
		EMX N=20	MX N=20	EMX N=20	MX N=20
Hair Density% change (hair/cm²)	Mean	33.7	24.2	19.95	8.65
	SD	18.49	16.11	23.16	11.2
	p value	0.09		0.16	
Hair thickness% change (µm)	Mean	9.1	3.35	5.9	8.3
	SD	12.93	10.61	9.52	10.66
	p value	0.10		0.91	
Hair(s)/ foll. Unit% change	Mean	15.56	12.3	8.35	6.75
	SD	15.8	13.92	15.24	11.29
	p value	0.57		0.73	
Baseline					
Hair Density (hair/cm²)	Mean	132.68	153.27	138.29	167.14
	SD	27.44	24.38	28.224	30.035
	p value	0.001 *		0.00*	
Hair Thickness (µm)	Mean	48.50	53.77	52	54.9
	SD	7.93	7.19	7.589	7.523
	p value	0.00*		0.012*	
Hair(s)/ fol. unit	Mean	1.70	2.14	1.726	2.212
	SD	0.207	0.281	0.161	0.34
	p value	0.00*		0.00*	

Table 6: Comparison between frontal and occipital regions absolute and percentile changes in trichoscopic features within EMX group and MX group at end of study period

		EMX		MX	
		Frontal N=20	**Occipital N=20**	**Frontal N=20**	**Occipital N=20**
Hair Density (hair/cm²)	Mean	+43	+27.95	+32.5	+12.8
	SD	21.036	29.237	21.80	18.82
	p value	0.067		0.01*	
Hair thickness (µm)	Mean	+4.2	+3.05	+1.6	+4.4
	SD	6.153	4.915	5.6	5.52
	p value	0.411		0.14	
Hair(s)/foll. unit	Mean	+0.253	+0.16	+0.212	+0.12
	SD	0.254	0.293	0.24	0.212
	p value	0.240		0.268	
Percentile changes					
Hair Density%change (hair/cm²)	Mean	33.7	19.95	24.2	8.65
	SD	18.494	23.16	16.13	11.62
	p value	0.033*		0.001*	
Hair thickness%change (µm)	Mean	9.1	5.9	3.35	8.3
	SD	12.937	9.525	10.61	10.66
	p value	0.286		0.2	
Av.hair per unit%change	Mean	15.65	8.35	12.3	6.75
	SD	15.816	15.246	13.92	11.29
	p value	0.130		0.17	

Table 7: Clinical photographic evaluation and Patients satisfaction at the end of the study by blinded dermatologists and reported side effects in both groups during the study

		EMX N=20	**MX N=20**
Mild improvement	N (%)	2(10%)	6(30%)
Moderate improvement	N (%)	9(45%)	10(50%)
Marked improvement	N (%)	9(45%)	4(20%)
	p value	0.137	
Slightly satisfied	N (%)	4(20%)	12(60%)
Moderately satisfied	N (%)	11(55%)	7(35%)
Greatly satisfied	N (%)	5(25%)	1(5%)
p value		0.023	
Side effects		Estradiol /Minoxidil N=20	Minoxidil N=20
Menstrual irregularity	N (%)	11 (55%)	1 (5%)
	p value	<0.001*	
Irritation/itching	N (%)	4(20%)	4(20%)
	p value	1.00	
Headache	N (%)	1(5%)	4(20%)
	p value	0.342	

Table 8: Correlation between change in frontal region and disease duration in both groups

		Duration	
		EMX group N= 20	**MX group N=20**
Hair density change (hair/cm²)	r value	0.175	0.094
	p value	0.462	0.694
Hair thickness change (µm)	r value	0.197	-0.267
	p value	0.405	0.255
Av. hair per unit change	r value	0.203	-0.266
	p value	0.392	0.257
Hair density% change(hair/cm²)	r value	0.328	0.185
	p value	0.158	0.434
Hair thickness% change (µm)	r value	0.256	-0.261
	p value	0.275	0.266
Av. hair per unit% change	r value	0.208	-0.230
	p value	0.378	0.330

Table 9: Relation between changes in frontal region and disease disease severity within EMX group and MX group

		Hair density change (hair/cm²)	Hair thickness change (µm)	Av. Hair per unit change	Hair density% change (hair/cm²)	Hair thickness% change (µm)	Av. Hair per unit% change
EMX group							
Mild N=8	Mean	+36.63	+5.25	+0.243	26.50	9.38	14.13
	SD	14.63	5.2	0.256	11.27	9.62	14.85
Moderate N=7	Mean	+49.57	+2.29	+0.259	36.14	6	16.29
	SD	28.26	7.95	0.353	22.92	16.29	22.66
Severe N=5	Mean	+44	+5.2	+0.260	41.8	3	17.20
	SD	17.95	5.16	0.0735	20.43	14.08	4.76
p value		0.899	0.814	0697	0.366	0.878	0.679
MX group							
Mild N=11	Mean	+32.64	+3.64	+0.296	23.27	7	17.18
	SD	21.24	5.66	0.226	15.55	10.81	12.68
Moderate N=5	Mean	+42.4	-1.80	+0.136	31.2	3	8.40
	SD	22.96	5.45	0.206	16.91	10.22	12.34
Severe N=4	Mean	+19.75	+0.25	+0.073	18	1.25	3.75
	SD	20.58	3.948	0.278	17.9	7.89	16.66
p value		0.365	0.166	0.195	0.44	0.182	0.223

Discussion

Trichoscopy, which is the dermoscopic imaging of the scalp and hair, validates the diagnosis and only rarely a biopsy may be necessary to separate androgenetic alopecia from chronic telogen effluvium or alopecia incognita [3]. The peripilar sign (PPS), the preponderance of single hair pilosebaceous units, the diversity of hair shaft diameters with an increased frequency of miniaturised vellus hairs, particularly in the frontoparietal region, and the yellow dots are the primary trichoscopic findings of AGA [5].

Our final analysis showed that all recruited patients significantly improved as regards hair density, thickness and average hair(s)/ unit in both frontal and occipital areas. The overall improvement was significantly high denoting the high efficacy of both formulations.

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. Similar results were also documented by Georgala *et al.* [15] where 30% of cases receiving 0.03% topical estradiol valerate solution showed improvement in anagen to telogen ratio in comparison to placebo. This was revisited again by Kim *et al.* [16] where they determined effectiveness and safety of commercial EllCranell® topical 0.025% alpha estradiol solution on 53 Korean women with FPHL. Similar to our findings, the latter study exhibited significant increase in hair density and hair thickness by photo-trichogram after 8 months of treatment.

These aforementioned studies concluded that topical estrogen preparations are effective in treatment of FPHL, and this was in agreement with our results which showed improvement in hair density, thickness and number of hairs per follicular unit within EMX group and this improvement was higher than MX group, although non-significant; denoting that the added ethinylestradiol might be responsible for this better response. Nonetheless, the former 2 studies differed from our study in using trichogram for evaluation instead of trichoscopy and the follow up parameter was anagen to telogen ratio in contrast to hair density, thickness and average hair(s) per unit. Also, all these studies used topical estrogen rather than an EMX preparation.

Moreover, ethinylestradiol in our study differs structurally from alfatradiol in the presence of ethynyl group at C17, which increases the estrogenic activity of ethinylestradiol. The study by Georgala *et al.* [15], only included post-menopausal females in contrast to our study that included females from 18 to 55 years with only one post-menopausal female.

Within EMX group; our results exhibited significant enhancement of frontal hair density, thickness and average hair (s)/ irrespective to disease severity which was in agreement with the results of the research executed by Cheo *et al.* [13], to determine efficacy of topical 0.025% 17α-estradiol and 3% minoxidil solutions on 34 Korean females for 6 months. Evaluation was done by phototrichogram and most of their patients indicated significant increase in hair count and hair thickness ($p< 0.0001$ and 0.001 respectively). However, the EMX formulation showed no statistically significant superiority over MX alone in our study.

As expected, within the MX group, we showed significant improvement of frontal hair density and average hair(s)/unit from baseline to week 24. This agreed with the comparative clinical trial executed by Blume-Peytavi *et al.* [17] to compare the efficacy of topical minoxidil 2% versus topical alfatradiol 0.025% on FPHL. Their results showed that topical treatment with 2% minoxidil solution for 6 months led to a significant rise in absolute hair density ($p \leq 0.0025$). However, the latter study reported significant rise in hair thickness with minoxidil 2% ($p < 0.0001$) which we did not observe in our MX group. On the other hand, hair density and thickness decreased or remained unchanged within the alfatradiol group after 6 months of treatment [17].

Interestingly, in the current work, both treatments (EMX and MX) significantly improved occipital hair density, thickness and number of hairs per unit from baseline to week 24. Although, the improvement was higher in EMX group, no statistically significant superiority was found for one modality over the other. However, Dhurat *et al.* [3], showed increased anagen hair in occipital scalp with topical minoxidil 5% for 6 months in males with AGA. We also compared fontal changes to occipital changes within each group. Our results showed a tendency for a higher percentile rise in hair counts on frontal vs occipital regions at end of treatment with both treatment modalities. On the other hand, such changes may not be as extensive, as evidenced by the difference in baseline trichoscopic features between frontal and occipital regions within the two study groups where hair

density, thickness and average number of hair(s) per unit were significantly higher on the occipital region ($p<0.05$).

None of the aforementioned studies reported menstrual irregularities with topical estradiol except the study conducted by Georgala *et al*. [15], 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. In contrast, we observed that menstrual side effects were significantly higher among EMX group patients (p =0.00).Two cases (10%) documented secondary amenorrhea, one of them (28 years old) after 3 months of treatment, lasted for 2 months and returned to regularity 2 weeks before treatment stoppage, and the other case (46 years old) after 4 months, lasted 3 months and then had polymenorrhea after 1 month of treatment cessation, then experienced secondary amenorrhea again for 3 months (she may have coincident beginning of premenopausal menstrual irregularities).

There was no significant connection between disease duration or severity and clinical response in both groups denoting that the two formulations are effective in all stages and that duration of disease is not associated with worse prognosis. Similar results were previously reported in the literature regarding minoxidil alone and minoxidil mixed with alfatradiol [13, 17].

Although the blinded dermatologist evaluation of improvement at end of study period did not differ statistically between both groups (p =0.137), a greater percentage of patients in EMX group (45%) were scored as achieving excellent improvement in contrast to MX group (20%). Choe *et al*. [13], also reported that 29% of their patients showed great improvement a after 6 months of using topical 0.025% 17α-estradiol solution in the morning and 3% minoxidil at night.

Unsurprisingly, the patients' satisfaction evaluation, performed at end of study period, showed a significantly higher satisfaction among patients in the EMX group (p =0.02). This may reflect the gross improvement in visible hair parameters as perceived by the patients themselves. In brief, our final analysis showed that in the frontal region, both EMX and MX effectively improve hair counts, thickness and number of hair(s)/ follicle after 6 months of treatment with no statistically significant differences between the 2 modalities. However, when we compared changes in hair diameters from baseline to end of treatment, only the EMX group indicated a statistically significant rise in hair thickness.

The relatively short period and small sample size were limitations in our study. Larger sample size may yield different results regarding hair thickness improvement. We recommend longer treatment period, larger sample size and more investigations for better evaluation of efficacy and safety. Also, a longer treatment period as well as follow-up period is warranted to verify the nature of the menstrual irregularities, we observed in our patients in the EMX arm.

Conclusions

Our understanding is that both study preparations (Ethinylestradiol 0.01% mixed with minoxidil 2% and minoxidil 2% alone) were almost equally effective in enhancement of hair growth in FPHL with superiority of the minoxidil only preparation regarding tolerability with less side effects during the treatment duration. Lower concentrations and different pharmacological formulation of ethinylestradiol is recommended for further studies. Although, EMX showed better clinical and dermoscopic results, as well as better patient satisfaction, this difference was not statistically significant. Together with the significantly higher incidence of menstrual adverse events, we cannot recommend using EMX for treating FPHL.

Acknowledgments: None to declare

Funding: None to declare

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How to Cite This Article
Ramzy NM, Mohammad AR. Effectiveness of combined topical ethinylestradiol and minoxidil versus minoxidil alone in treating female pattern hair loss. International Journal of Dermatology Research. 2023; 6(1): 32-39.