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Treatment of female pattern hair loss with oral antiandrogens

R. Sinclair,*† M. Wewerinke‡ and D. Jolley§

*University of Melbourne Department of Dermatology, St Vincent's Hospital, 41 Victoria Parade, Fitzroy 3065, Melbourne, Australia
†Department of Medicine, Monash University, Melbourne, Australia
‡School of Medicine, University of Groningen, the Netherlands
§School of Health Sciences, Deakin University, Melbourne, Australia

Correspondence
Rodney Sinclair
E-mail: sinclair@svhm.org.au

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Summary

Background It has not been conclusively established that female pattern hair loss (FPHL) is either due to androgens or responsive to oral antiandrogen therapy.
Objectives To evaluate the efficacy of oral antiandrogen therapy in the management of women with FPHL using standardized photographic techniques (Canfield Scientific), and to identify clinical and histological parameters predictive of clinical response.
Methods For this single-centre, before–after, open intervention study, 80 women aged between 12 and 79 years, with FPHL and biopsy-confirmed hair follicle miniaturization [terminal/vellus (T/V) hair ratio $\leq 4:1$] were photographed at baseline and again after receiving a minimum of 12 months of oral antiandrogen therapy. Forty women received spironolactone 200 mg daily and 40 women received cyproterone acetate, either 50 mg daily or 100 mg for 10 days per month if premenopausal. Women using topical minoxidil were excluded. Standardized photographs of the midfrontal and vertex scalp were taken with the head positioned in a stereotactic device. Images were evaluated by a panel of three clinicians experienced in the assessment of FPHL, blinded to patient details and treatment and using a three-point scale.
Results As there was no significant difference in the results or the trend between spironolactone and cyproterone acetate the results were combined. Thirty-five (44%) women had hair regrowth, 35 (44%) had no clear change in hair density before and after treatment, and 10 (12%) experienced continuing hair loss during the treatment period. Ordinal logistic regression analysis to identify predictors of response revealed no influence of patient age, menopause status, serum ferritin, serum hormone levels, clinical stage (Ludwig) or histological parameters such as T/V ratio or fibrosis. The only significant predictor was midscalp clinical grade, with higher-scale values associated with a greater response ($P = 0{\cdot}013$).
Conclusion Eighty-eight percent of women receiving oral antiandrogens could expect to see no progression of their FPHL or improvement. High midscalp clinical grade was the only predictor of response identified. A placebo-controlled study is required to compare this outcome to the natural history of FPHL.

Male pattern hair loss (MPHL) is clearly androgen-dependent, responds to antiandrogens and is associated with polymorphisms on the androgen receptor gene.[1] The condition has a high degree of hereditability[2] and there is little evidence for environmental influences on MPHL.[3] MPHL produces either bitemporal recession or vertex balding or midfrontal diffuse hair thinning progressing to baldness or a combination of the three. The degree of bitemporal recession does not correlate with presence or severity of midfrontal or vertex scalp hair loss.[4]

In contrast, neither the androgen-dependent nature nor the genetic basis of female pattern hair loss (FPHL) has been

clearly established. The role of environmental factors, such as thyroid disease and decreased serum ferritin is debated.[5–7] FPHL may present with diffuse reduction in hair density on the crown, increased telogen hair shedding or both.[8]

Women who present with a reduction in hair density often have a 'Christmas tree' pattern of hair loss in the midline part.[9] The frontal hairline may or may not be preserved,[10,11] however, as with MPHL, the degree of bitemporal recession does not correlate with the presence or severity of midfrontal scalp hair loss.[12]

Women who present with increased telogen hair shedding of more than 6 months' duration without any discernable reduction in hair density over the crown may have either chronic telogen effluvium (CTE) or FPHL.[13] CTE is a diagnosis of exclusion and a scalp biopsy is required to differentiate CTE from early FPHL.[14] Subjects with CTE may confound therapeutic trials for FPHL and at least one 4-mm punch biopsy specimen for horizontal sectioning is recommended for each subject prior to enrolment.[15]

Current treatments for FPHL include topical minoxidil,[16] spironolactone and cyproterone acetate.[11,17–20]

Spironolactone and cyproterone acetate are both antiandrogens competing with androgens for high-affinity androgen receptors. They have a similar molecular structure, with a basic steroid structure of three hexanes and a pentane ring.

Spironolactone has an acetylthio substitution at position 7 and is an aldosterone antagonist used primarily as a potassium-sparing diuretic and antihypertensive. It also acts as an antiandrogen by competitively blocking androgen receptors as well as inhibiting ovarian androgen production[8] and has been successfully used in doses of 50–300 mg day^{-1} in acne and hirsutes.[21] Potential side-effects include postural hypotension, electrolyte imbalance, especially in the context of renal impairment, menstrual irregularity, fatigue and urticaria.[8]

Cyproterone acetate is an androgen receptor blocker with strong progestational activity and a weak glucocorticoid action. In FPHL it decreases hair shedding,[22] but there is generally no visually significant regrowth.[23] Cyproterone acetate is not approved by the U.S. Food and Drug Administration. The dose required for premenopausal women is 100 mg daily for 10 days of each menstrual cycle.[20] Postmenopausal women use 50 mg daily continuously. Potential side-effects are dose-related and include menstrual irregularity, weight gain, breast tenderness, loss of libido, depression and nausea.[8]

A number of recent case series suggest finasteride[24,25] and flutemide[26] may also have efficacy in the treatment of FPHL; however, finasteride is contraindicated in women of childbearing potential and flutemide carries the risk of severe liver toxicity. A 12-month, randomized, double-blinded placebo-controlled study of postmenopausal women with FPHL failed to demonstrate superiority of finasteride over placebo.[27]

Although Ludwig[11] asserted in 1977 that treatment with antiandrogens in the early stages can arrest or at least retard the progress of FPHL, there have been few published case series. Possible explanations for the limited and often conflicting efficacy data pertaining to the use of antiandrogens in FPHL include absence of biopsy-proven diagnosis, difficulties using currently available clinical grading scales and a variable and often inadequate methodology for evaluation of treatment response.[28]

The purpose of this study is to investigate the efficacy of antiandrogen monotherapy for women with FPHL and histological evidence of androgenetic alopecia on scalp biopsy using standardized photographic documentation,[29] and to identify clinical and histological parameters predictive of clinical response.

Materials and methods

Case selection

Data was analysed from 80 women aged between 12 and 79 years who had been referred to a specialist hair clinic for investigation and treatment of hair loss of greater than 6 months' duration. All patients were examined by a specialist dermatologist (R.S.) to exclude other hair loss disorders such as cicatricial alopecia, traction alopecia and trichotillomania or alopecia areata. Hair density was rated according to a modified scale that assessed the central part over the midscalp (Fig. 1).

Screening haematological investigations were performed to exclude thyroid disease, iron deficiency, zinc deficiency, systemic lupus erythematosus and hormone dysregulation. All patients had three 4-mm punch biopsies taken from the vertex scalp for horizontal sectioning to assess the terminal/vellus hair ratio (T/V). Only women with a T/V $\leq$ 4:1 were included in the analysis.

The mean duration of treatment was 16 months. All women were treated for a minimum of 12 months. Forty women received oral spironolactone 200 mg day^{-1}. Forty women received with cyproterone acetate. Postmenopausal women (22) received 50 mg daily continuously. Premenopausal women (18) took 100 mg daily for 10 days each month together with a combination oral contraceptive pill. All women of childbearing potential using oral antiandrogens were counselled about the need to avoid pregnancy and effective forms of contraception. All women were instructed not to use topical minoxidil.

Scalp photography

All participants had serial standardized scalp photography of the frontal scalp and vertex scalp at 6-monthly intervals with a Nikon E3 digital camera with a 105 mm f2·8 lens and a CSS Twin Flash. The patient's head was placed in a stereotactic device to ensure consistency of patient positioning and photographic distance.[29] For the frontal global photograph, each patient has her hair parted centrally to optimally view the midline part. For the vertex photograph the hair is combed away from the crown. The system is identical to that used in phase II and III clinical trials in men receiving finasteride for androgenetic alopecia,[30,31] and has been previously validated.[32]

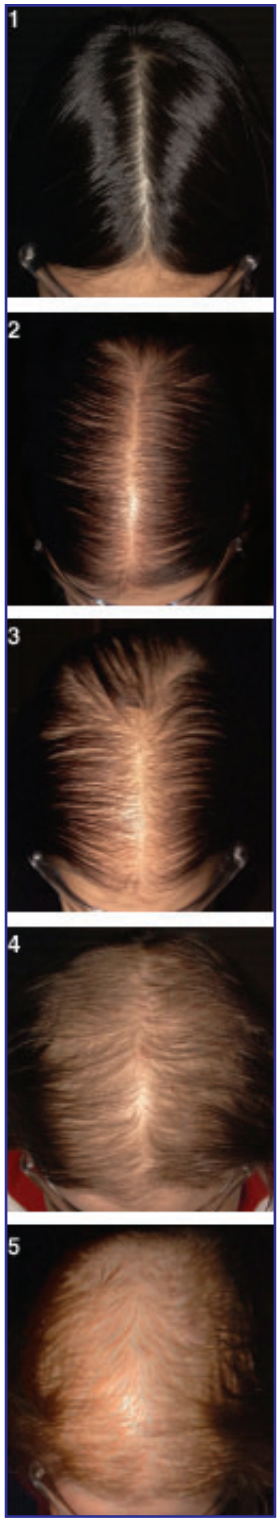

Fig 1. Midscalp clinical grade. A five-point visual analogue scale for assessment of female hair loss.

Patient demographic data

Clinical features recorded for analysis included patient age, menopause status, duration of hair loss prior to initiation of treatment, stage of hair loss at presentation using both the Ludwig scale and the midscalp clinical grading scale, treatment and duration of treatment.

Scalp biopsy

An area on the central midscalp was selected for biopsy and the skin marked with a surgical pen. If the patient parted her hair centrally, the site was shifted 1–2 cm laterally to avoid producing a scar in the part line. The skin was infiltrated with 2 mL of 2% lignocaine with 1 in 80 000 adrenaline (Astra Pharmaceuticals, Pty. Ltd, North Ryde NSW, Australia), and after a period of 10 min a 4-mm disposable punch biopsy (Stiefel Laboratories, Bruckenstrasse, Wachterbach, Germany; supplied from Castle Hill, NSW, Australia) was used to take the biopsies. Three plugs of immediately adjacent skin in an anterior–posterior line were taken and all sent for horizontal section. The wound was closed primarily with 2-O nylon suture material (Ethicon, Johnson & Johnson, North Ryde NSW, Australia), and the sutures removed after 7–10 days.

The biopsies were fixed in 10% neutral buffered formalin solution. For horizontal sectioning the biopsy was bisected horizontally 1 mm below the dermoepidermal junction at the approximate entry of the sebaceous ducts into the follicle and the two portions embedded side by side, with the freshly cut sections face down in the block. Four slides containing three paired sections each were generally sufficient for evaluation of the horizontal section, but additional deeper sections were obtained if the initial section was too high or low. Vertical sections were bisected vertically centrally. All sections were stained with haematoxylin and eosin for light microscopy. The total hair count was determined along with the total terminal hair count and the vellus-like hair count at the mid isthmus level by a single observer. The ratio of terminal to vellus-like hairs could then be calculated. A ratio of $\leq 4:1$ was considered diagnostic of FPHL.[33]

Midscalp clinical grading scale

The midscalp clinical grading scale was developed from images within the database of midscalp photographs and used to clinically grade women undergoing treatment for hair loss. The five-point visual analogue grading scale has been tested for interobserver reproducibility[34] and has also been evaluated for patient self-assessment.[35]

Laboratory investigations

All patients had a baseline full blood count, iron status (serum ferritin), serum zinc, liver and renal function tests, thyroid function tests, serum testosterone, serum dihydroepiandostenedione sulphate (DHEAS), serum sex hormone binding globulin (SHBG), serum lutenizing hormone and follicle stimulating hormone.

Evaluation of efficacy

A number of investigational tools have emerged over recent years and have been evaluated.[28] None is perfect. The methods with the greatest reliability are global photographs and hair counts obtained from colour macrophotographs. Previous studies have shown excellent concordance between hair count results and global photographic assessment, and both are superior to patient self-assessment and investigator assessment. Global photographs were used in this study as the only endpoint due to their reproducibility,[32] ease of use and correlation with a meaningful outcome from the patient's perspective, namely visible regrowth of hair.

Statistical analysis

Global photographic assessment was the primary efficacy endpoint. Frontal and vertex photographs were arranged and presented to a panel of three clinicians who were blinded to patient details and treatment. The panel evaluated hair growth or loss by comparing baseline photographs with the most recent follow-up photographs of each patient. The frontal and vertex photos were evaluated independently. A three-point rating scale was used: clearly improved hair density (+), no discernible difference (0) and clearly decreased hair density (–). Good concordance (83·3%) was achieved using this three-point scale. For internal validation the assessment procedure was repeated after 2 weeks. Concordance was 85% within each dermatologist.

Patient age, menopause status, serum ferritin, serum hormone levels, clinical stage using the Ludwig scale and also the midscalp clinical grading scale and histological parameters such as T/V ratio and the presence or absence of fibrosis were considered potential predictors of treatment response.

To evaluate the predictors of response, the sum of the frontal and vertex response was coded from −2 to +2 in increasing strength. The analysis method used for this type of outcome variable was ordinal logistic regression. This exploits the ordered nature of the outcome variable ($-2 < -1 < 0 < +1 < +2$), but makes no assumptions about the relative distances between these ordered values.

Results

Patient demographics

Eighty women with clinical and histological evidence of FPHL were evaluated in this study. The baseline characteristics are shown in Table 1. Forty women received spironolactone. Eleven were postmenopausal and were commenced on 200 mg day^{-1}. In five cases the dose was reduced to 100 mg day^{-1} due to intolerance of the higher dose. Twenty-nine were premenopausal and took either 200 mg day^{-1}, either alone (16 women) or in conjunction with an oral contraceptive pill (13 women). Forty women received cyproterone acetate. Eighteen women were premenopausal and took cyproterone acetate 100 mg mg day^{-1} from days 5 to 15 of the menstrual cycle in combination with a combined oral contraceptive pill. Twenty-two women were postmenopausal and took cyproterone acetate 50 mg day^{-1} continuously, either alone (10 women) or in conjunction with premarin 0·625 mg day^{-1} (12 women).

Table 1 Baseline characteristics of women included in the study

	Antiandrogen study (n = 80)
Mean age	46 ± 16·1 (range 17–79)
Menopause status	46 (58%) premenopausal
	34 (42%) postmenopausal
Mean duration of hair	50 ± 64·1 months
loss prior to presentation	(range 2–360 months)
Baseline Ludwig score	
I	47 (59%)
II	32 (40%)
III	1 (1%)
Midscalp clinical grade	
1	11 (14%)
2	22 (28%)
3	18 (22%)
4	24 (30%)
5	5 (6%)
Histological parameters	
Mean baseline T/V hair count	2·6 ± 0·8
T/V ≤ 2 : 1	17 (21%)
T/V ≤ 3 : 1 but > 2 : 1	37 (46%)
T/V ≤ 4 : 1 but > 3 : 1	26 (33%)
Fibrosis	present 12 (15%)
	absent 68 (85%)

T/V, terminal to vellus ratio.

The average duration of treatment was 16 months with a SD of 4·6. All women had serum ferritin > 20 μg mL^{-1}. Five women had stable treated hypothyroidism and were euthyroid. Four out of 80 women had an elevated free androgen index. In three cases this was due to a low sex hormone binding globulin. In one case the serum testosterone level was elevated, and this patient was known to have polycystic ovary syndrome. No blood test outcome variable was useful for predicting treatment response and these were not included in further statistical analysis.

Standardized scalp photography assessment

To analyse the response to treatment, responses of the vertex and frontal areas of the scalp were coded as −1, 0, +1 and then summed to create a single dimensional variable of response (Resp-both).

There was no discernible difference in results between spironolactone and cyproterone acetate (Table 2) or the trend between these two agents and so the results were combined (Table 3). Of the 80 women there were then 16 who were recorded as 'improved' for both the frontal and vertex (score = 2) areas of the scalp, 19 who improved in one area,

Table 2 Patient response to spironolactone treatment (and cyproterone acetate treatment)

	Resp-v			
Resp-f	–	0	+	Total
–	1 (2)	3 (2)	0 (0)	4 (4)
0	1 (1)	17 (18)	4 (3)	22 (22)
+	0 (0)	5 (7)	9 (7)	14 (14)
Total	2 (3)	25 (27)	13 (10)	40 (40)

Resp-f, photographic assessment of response of frontal scalp; Resp-v, photographic assessment of response of vertex scalp.

Table 3 Patient response to antiandrogen treatment

	Resp-v			
Resp-f	–	0	+	Total
–	3	5	0	8
0	2	35	7	44
+	0	12	16	28
Total	5	52	23	80

Resp-f, photographic assessment of response of frontal scalp; Resp-v, photographic assessment of response of vertex scalp.

but not in the other (score +1) and 35 (44%) who had no change in either area (score 0). Seven women deteriorated in one area but saw no change in the other (score = −1) and three were worse off with both (score = −2). No woman improved in one area and deteriorated in the other. (Table 4). In responders with extended follow-up, the improvement seemed incremental at each 6-month interval (Figs 2 and 3).

Multivariate analysis

In our study, only one of the predictors was significantly associated with response outcome, the midscalp clinical grade. Midscalp clinical grades of 3 or 4 had significantly different responses from a midscalp clinical grade of 1 ($P = 0{\cdot}041$ and $P = 0{\cdot}013$, respectively). There was a significant association between midscalp clinical grade and response to treatment ($P = 0{\cdot}013$). In a cross-tabulation of midscalp clinical grade against the combined response variable it is clear that higher midscalp clinical grades give higher responses (Table 5).

The P-values for all the other predictor variables, namely patient age, menopausal status, duration of hair loss, family history of hair loss, iron status, thyroid function, serum hormone levels and scalp histological parameters were greater than 0·05, indicating no statistically significant association with the ordered response variable.

A boxplot or response to treatment by age and menopause status showed the response to be uniform across age and menopause status (Fig. 4).

Table 4 Comparison of frontal response to total response. No woman improved in one area and deteriorated in another

	Resp-f			
Resp-both	–	0	+	Total
− 2	3			3
− 1	5	2		7
0		35		35
1		7	12	19
2			16	16

Resp-both, additive score of Resp-f and Resp-v.

Discussion

In this study, treatment with the oral antiandrogens spironolactone or cyproterone acetate produced similar improvement in scalp hair in women with biopsy proven FPHL. Of the 80 women included in this study, there were 35 (44%) with hair regrowth in either the frontal or vertex areas of the scalp or in both areas. Another 35 (44%) had no clear difference in hair density before and after treatment and only 10 (12%) had hair loss in one or both areas. The average duration of treatment was 16 months.

Patterned hair loss is a chronic progressive condition in both men and women. Using global photography Price[18] demonstrated decreased hair density in 13% of 70 women on placebo at 12 months, while Kaufman *et al.* showed that in men, 7% on placebo have decreased hair density on scalp photography at 12 months, 33% at 24 months, 69% at 36 months and 75% of men at 60 months.[36] As such, prevention of further hair loss can be considered a positive treatment outcome.

If we define a response to treatment as prevention of hair loss and/or regrowth of hair then in this study 88% of the women with androgenetic alopecia had a positive response to oral antiandrogen therapy with both agents used, spironolactone or cyproterone acetate, being equally effective.

Twelve per cent of women had progressive hair loss while receiving antiandrogen therapy. Possible reasons include poor compliance with the treatment, inadequate dose, incorrect diagnosis and disease response heterogeneity. A similar number of men treated with finasteride for MPHL fail to respond to therapy.[30,31]

Previous studies investigating the use of oral antiandrogens have produced conflicting results. Peereboom-Wynia *et al.*[22] found an improvement in the trichogram findings among women with FPHL receiving 20 mg day^{-1} of cyproterone for 15 days each month, but not in controls. Trichograms are of only limited value in the assessment of treatment response. Mortimer *et al.*[37] reported a beneficial effect of cyproterone 100 mg day^{-1} for 10 days each month when assessed using phototrichograms, a more accurate measure or response.

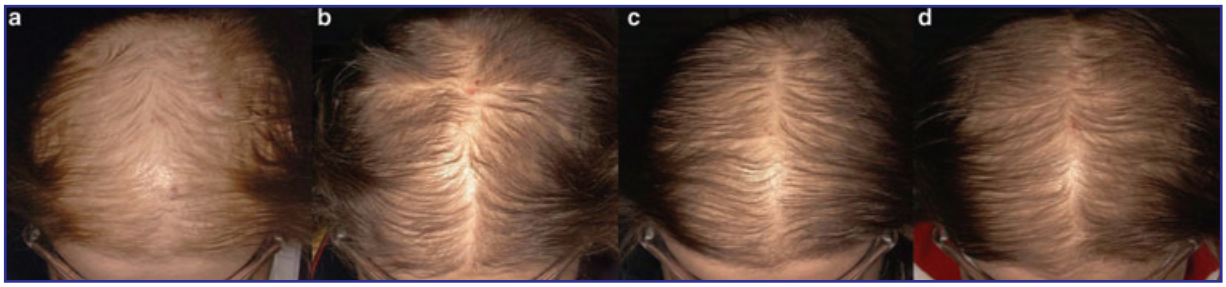

Fig 2. Response to cyproterone acetate over 24 months. (a) Baseline. (b) 6 months. (c) 12 months. (d) 24 months.

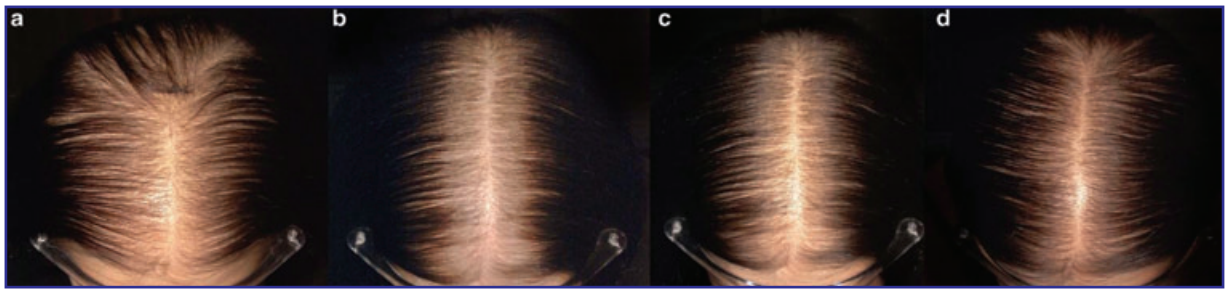

Fig 3. Response to spironolactone over 24 months. (a) Baseline. (b) 6 months. (c) 12 months. (d) 24 months.

Table 5 Cross-tabulation of midscalp clinical grade against the combined response

	Midscalp clinical grade				
Resp-both	1	2	3	4	5
− 2	1		2		
− 1	1	2	2	2	
0	8	12	4	8	3
1	1	6	4	8	
2		2	6	6	2

Resp-both, additive score of Resp-f and Resp-v.

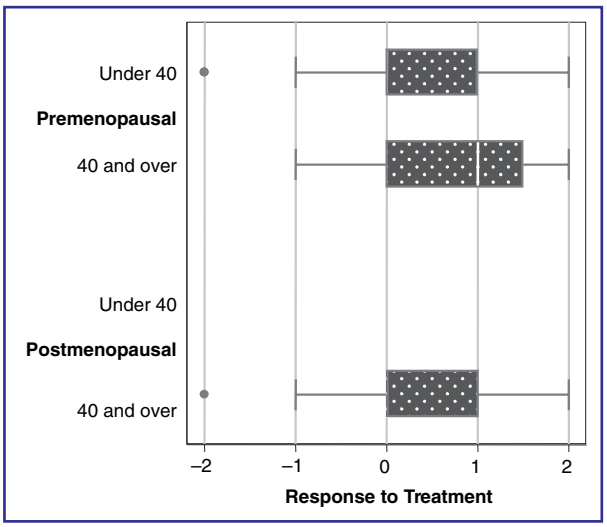

Fig 4. Boxplot of treatment response by age and by menopause status, clearly shows the uniformity of the response across age and menopause status.

Dawber *et al.*[20] used a similar dose and found both subjective improvements in patients receiving treatment and also an objective increase in hair diameter. While patients' subjective assessments are notoriously unreliable, hair diameter is a surrogate marker of hair follicle miniaturization that has been proven useful in the assessment of response of hirsutes to antiandrogens. It has only a limited track record in the evaluation of FPHL.

In contrast Carima and Lobo[26] were unable to demonstrate any clinical improvement in 12 patients with a clinical diagnosis of FPHL who received cyproterone acetate 50 mg with ethinyl oestradiol in a reverse sequential regimen. Vexiau *et al.*[23] were unable to identify an improvement in the mean hair density as assessed by phototrichograms in 25 patients with FPHL who completed 12 months' treatment with cyproterone 50 mg daily for 20 days each month, although they did identify a subgroup of women who did well with cyproterone. Inclusion criteria for this study were a clinical diagnosis of FPHL. Over two-thirds of the patients included had Ludwig stage I hair loss and it is possible that some patients may have had chronic telogen effluvium and contaminated the results, thereby explaining the discrepancy between our results.

The other objective of this study was to identify clinical and histological features that predict response to treatment. The variables of age, menopause status, duration of hair loss, clinical stage as assessed by both the Ludwig scale and the

midscalp clinical grading scale, T/V ratio, total vellus hair count, fibrosis, drug and duration of treatment were assessed.

The only variable with a significant association to response was the midscalp clinical grade. Women with higher grades indicating more advanced hair loss will respond better to therapy. This may reflect the limitations of the primary endpoint used to evaluate the response to treatment. It is not possible to observe photographic improvement in women enrolled with stage 1 hair loss using the midscalp clinical grading scales.

The androgen-dependent nature of MPHL has been clearly established with a majority of men demonstrating increased hair growth or arrested progression of hair loss with finasteride, a type 2 5α reductase enzyme inhibitor that decreases levels of dihydrotestosterone in both serum and tissue.[31] In women, diffuse midfrontal scalp hair loss is generally regarded as the female equivalent of male androgenetic alopecia, although this has recently become contentious[38–40] with the publication of a trial showing a poor response of postmenopausal women with FPHL to finasteride.[27]

While most women in this study had no clinical or biochemical evidence of hyperandrogenism,[1] the response of this cohort of women to oral antiandrogen therapy supports the view that androgens play an important role in the pathogenesis of FPHL. We advocate a placebo-controlled study to compare this outcome with the natural history of FPHL, and also genetic research to investigate whether identified genetic polymorphisms on the androgen receptor implicated in MPHL[41] are also relevant in FPHL.[42]

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