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**Female pattern hair loss: A pilot study investigating combination therapy with low dose oral minoxidil and spironolactone**

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**Conflict of Interest:** Rodney Sinclair holds Innovation Patent 2011100917 entitled Treatment of male and female androgenetic alopecia with oral minoxidil either alone or in combination with antiandrogens on 18 August 2011.

**Key Words:** female pattern hair loss, androgenetic alopecia, telogen effluvium,

### **Capsule summery**

- Oral minoxidil is an anti-hypertensive that causes hypertrichosis
- Spironolactone is a diuretic with antiandrogen properties used in the treatment of female pattern hair loss
- 100 women with female pattern hair loss were treated off-label with extemporaneously formulated oral capsules containing minoxidil 0.25mg and spironolactone 25mg
- Mean reduction in hair loss severity score was 0.85 at 6 months and 1.3 at 12 months. Mean reduction in hair shedding score was 2.3 at 6 months and 2.6 at 12 months
- Side effects were seen in 8 patients and included postural hypotension, hypertrichosis, and urticaria.

### **Abbreviations:**

FPHL, female pattern hair loss

### **ABSTRACT (232 words)**

**Background:** Minoxidil and spironolactone are oral antihypertensives known to stimulate hair growth,

**Objective:** To report on case series of women with pattern hair loss (PHL) treated with once daily minoxidil 0.25 mg and spironolactone 25 mg.

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**Methods:** Women newly diagnosed with a Sinclair stage 2-5 PHL were scored for hair shedding and hair density before and after 12 months treatment with oral minoxidil 0.25 mg and spironolactone 25mg.

**Results:** 100 women were included in this observational pilot study. Mean age was 48.44 years (range 18-80). Mean hair loss severity at baseline was Sinclair 2.79 (range 2-5). Mean hair shedding score at baseline was 4.82. Mean duration of diagnosis was 6.5 years (range 0.5 -30). Mean reduction in hair loss severity score was 0.85 at 6 months and 1.3 at 12 months. Mean reduction in hair shedding score was 2.3 at 6 months and 2.6 at 12 months. Mean change in blood pressure was -4.52mmHg systolic and -6.48mmHg diastolic. Side effects were seen in 8 of women but were generally mild. No patients developed hyperkalaemia or any other blood test abnormality. Six of these women continued treatment and 2 women who developed urticaria discontinued treatment.

**Limitations:** Prospective uncontrolled open label observational study.

**Discussion:** Once daily capsules containing minoxidil 0.25mg and spironolactone 25 mg appear to be safe and effective in the treatment of FPHL. Placebo controlled studies to investigate this further are warranted.

## **Introduction**

Female pattern hair loss (FPHL) is one of the most common causes of hair loss encountered in clinical practice [1]. FPHL is a complex polygenic disorder [2, 3, 4, and 5] characterized clinically by diffuse hair thinning over the mid frontal scalp [6] and increased hair shedding [7]. Histologically the hallmark is site-specific hair follicle miniaturization. [8] Site specificity may result from epigenetic modification of the androgen receptor gene. [9] The proportion of miniaturized follicles increases with the severity of hair loss [10]. Age related, so-called senescent alopecia also shows hair follicle miniaturization and is indistinguishable from FPHL [11]. FPHL adversely impacts on quality of life [12]. FPHL is progressive and the risk, prevalence and severity of FPHL increase with age [13]. In a population study of over 700 women, FPHL, defined as  $\geq$  Sinclair stage 2, was found in 12% of women aged 20-29 and 57% of women aged  $\geq$  80. Severe hair loss, defined as Sinclair stages 3, 4 and 5, increased from 4% among women aged 20-29 years to 30% among women aged  $\geq$  80 years. In addition, some women present with increased hair shedding but no clinical evidence of

FPHL. Approximately 60% of these women will have histological evidence of androgenetic alopecia on scalp biopsy with a terminal to vellus hair ration  $\leq 4:1$  [14]. Hair follicle miniaturization is potentially reversible initially, but eventually becomes irreversible [15, 16, and 17]. One hypothesis to explain irreversible hair follicle miniaturization is the observed replacement of the proximal arrector pili muscle by adipose tissue disrupting the stem cell niche at the hair follicle bulge [17, 18]. Fatty degeneration of the arrector muscle is not seen in alopecia areata where hair follicle miniaturization is potentially reversible [18]. Treatment is likely to be most successful in women with early female pattern hair loss [19].

While scalp biopsy may be required to identify histological features of androgenetic alopecia in women with early FPHL and differentiate this condition from chronic telogen effluvium [20], dermoscopy is a valuable alternative and shows a reduction in the number of secondary hair fibres emerging from each pore over the affected region of the scalp [17,21]

A number of agents have also been used in the treatment of female pattern hair loss including the androgen receptor antagonists spironolactone, cyproterone acetate [19] and flutamide [22] as well as the  $5\alpha$  reductase antagonist finasteride [23] and dutasteride. These agents can be used either alone or in combination with topical minoxidil. [24]

Minoxidil is a piperidinopyrimidine derivative and a potent vasodilator that is effective orally for severe hypertension. When applied topically, minoxidil has been shown to arrest hair loss or to induce mild to moderate hair regrowth in approximately 60% of women with FPHL [25]. A clinical trial comparing 5% and 2% formulations of minoxidil found a mean increase in non-vellus hair counts after 48 weeks of 18% and 14%, respectively [26]. Topical minoxidil was approved by the FDA in 1992 for the treatment of female pattern hair loss. It appears to be a safe therapy with side effects only of local irritation and hypertrichosis of the temples, and there is a low incidence of contact dermatitis [27]. If treatment is stopped, clinical regression occurs within 6 months, to the state of baldness that would have existed if treatment had not been applied [28]. For patients to maintain any beneficial effect, applications must continue indefinitely.

Spironolactone is an aldosterone antagonist and has been used as a potassium-sparing diuretic for over 50 years. It is structurally a steroid, with basic steroid nuclei with four rings. Its primary metabolite, canrenone, is the active antagonist of aldosterone and

contributes to the diuretic action. The ingested drug is absorbed rapidly and metabolized by the liver to canrenone and potassium canrenoate. The drug is available in 25 mg and 100 mg tablets. No dermatologic indications for spironolactone have been approved by the FDA however it is widely used off-label in the treatment of FPHL [29] and has been shown to arrest progression in over 90% of women. In addition approximately 30% of women demonstrate improved hair density of global photography [19].

Hair transplantation surgery is a highly effective treatment for male pattern hair loss. For women surgical options are limited. Most women with FPHL also have reduced hair density over the occipital scalp reducing the yield from hair transplant surgery.

We report the results of a prospective, uncontrolled observational study of the safety and usefulness of a single once daily low dose oral minoxidil in combination with spironolactone in the treatment of FPHL.

## **Methods**

Women with a Sinclair stage 2-5 female pattern hair loss were offered treatment with a single once daily capsule containing minoxidil 0.25 mg together with spironolactone 25 mg. For women with a baseline blood pressure  $\leq 90/60$  or a past history of postural hypertension or fainting 50mg of sodium chloride was added to the capsule. Hair shedding was scored using a 6 point visual analogue scale (figure 1). Hair density was scored using the 5 stage Sinclair scale (figure 2). Women were reviewed at 3 monthly intervals. Blood pressure was recorded at each visit and patients were specifically questioned about the presence of unwanted facial or body hair at each follow-up visit and any other side-effects.

Full blood count, renal function, electrolytes and liver function testing was performed at baseline and at 3 monthly intervals.

## **Results**

100 women with newly diagnosed Sinclair stage 2-5 female pattern hair loss were treated with a once daily capsule containing minoxidil 0.25 mg and spironolactone 25 mg and followed prospectively for 12 months

The mean age was 48.44 years (range 18-80). Mean hair loss severity at baseline was Sinclair 2.79 (range 2-5). The mean hair shedding score at baseline was 4.82 (range 1-6). Mean duration of diagnosis was 6.5 years (range 0.5 -30).

Side effects were seen in 8 of women but were generally mild. Side effects included urticaria (2), postural hypotension (2) and facial hypertrichosis (4). No patients developed hyperkalaemia or any other blood test abnormality. Six of these women continued treatment and 2 women who developed urticaria discontinued treatment.

Baseline mean systolic blood pressure was 122.92mmHg. Baseline mean diastolic pressure was 79.17mmHg. Follow up blood pressure after 3 months was 118.40 systolic and 72.69 diastolic. Mean change in systolic blood pressure was -4.52 mmHg. Mean change in diastolic blood pressure was -6.48. 2 patients developed symptoms of postural hypotension necessitating introduction of 50mg daily of sodium chloride.

Four patients reported hypertrichosis. This was managed by a combination of plucking (1), or waxing (3).

A temporary increase in hair shedding 3-6 weeks following initiation of treatment was anticipated. Twenty-two patients reported this shedding as being of significant concern. All patients had been pre-warned about the possibility of a temporary increase in hair shedding on initiation of therapy and advised to continue treatment. No women discontinued the treatment as a result of increased hair shedding following commencement of therapy. For 16 women this shedding ceased within 4 weeks, while for 4 women it persisted for more 6 weeks and for 2 women it persisted for more than 12 weeks.

Two patients ceased the medication due to urticaria that was presumed to be related to the spironolactone. The urticaria settled within 7 days of cessation and did not recur when the minoxidil was recommenced as monotherapy. .

Mean hair loss severity at baseline was Sinclair 2.79 (range 2-5). Mean hair shedding score at baseline was 4.82 (range 1-6).

Mean reduction in hair loss severity score was 0.1 at 3 months, 0.85 at 6 months, 1.1 at 9 months and 1.3 at 12 months (figure 3). Mean reduction in hair shedding score was 1.1 at 3 months, 2.3 at 6 months, 2.7 at 9 months and 2.6 at 12 months.

## **Discussion**

Oral minoxidil was approved by the FDA for the treatment of hypertension in 1979. It was first noticed to improve hair loss in male androgenetic alopecia in 1980 [30].

Topical minoxidil received FDA approval for male androgenetic alopecia in 1988 and for female pattern hair loss in 1992.

Oral minoxidil is not often used in the treatment of AGA, largely due to the side-effect profile seen at standard doses.

Our women's hair loss clinic was established in 1995 and currently treats over 750 women with FPHL. The mainstay of therapy was an oral antiandrogen such as cyproterone acetate or spironolactone used either alone [19] or together topical minoxidil [31] Over the years we had accumulated a number of women in our clinic that were either not satisfied with the results achieved by conventional therapy, or who were intolerant of topical minoxidil. Intolerance was either due to scalp irritation or altered hair texture. Oral minoxidil is available in Australia as 10mg tablets. Off label use of a half or quarter tablet of oral minoxidil led to noticeable improvement in hair density in most of these women, but was complicated by postural hypotension, fluid retention and hypertrichosis. While fluid retention can often be managed by the addition of spironolactone, this has the potential to increase postural hypotension.

As Minoxidil side-effects are all dose related, we compounded oral minoxidil extemporaneously into capsules containing 0.25 mg or one fortieth of a tablet.

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To reduce the risk of fluid retention and to augment therapy by the addition of an oral antiandrogen, spironolactone 25mg was added to the capsule. For women with low blood pressure, 50mg of sodium chloride was also added to the capsule. The combination of spironolactone and minoxidil is likely to have an additive benefit in FPHL [31].

Low dose oral minoxidil was well tolerated in the majority of our patients with FPHL and is a reasonable alternative in women intolerant of, or unwilling to use topical minoxidil. While hyperkalaemia, creatinine elevation and hepatitis are reported with spironolactone [32], we did not encounter any haematological abnormalities at the dose used in this study.

Most women noticed a reduction in hair shedding at 3 months and an increase in hair density at 6 months.

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Figure 1.

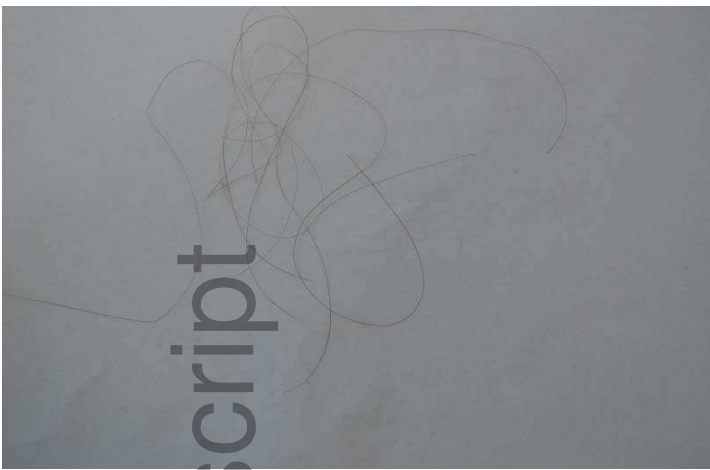
Sinclair hair shedding scale. Patients are asked how much hair they shed in a single day. As hair shedding is usually worse after washing that score was documented.

Figure 2

Sinclair hair loss severity scale for female pattern hair loss.

Figure 3.

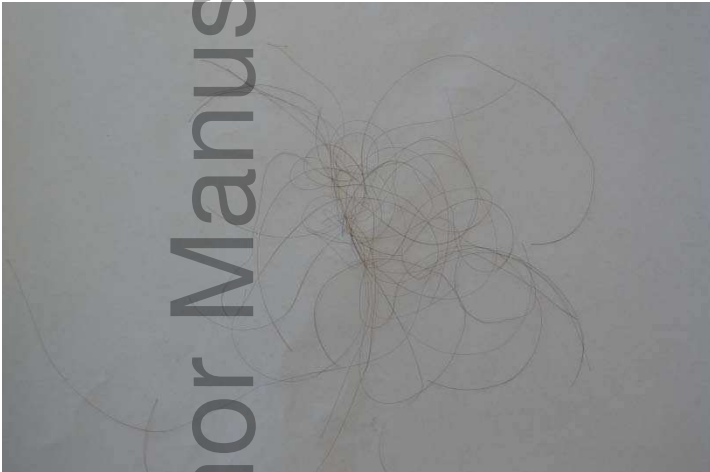
Before and after 12 months therapy.



1= 10



4= 200



2= 50



5= 400



3= 100



6= 750

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1



2



3



4



5

Patient 1



Patient 2



Patient 3



Patient 4



Patient 5

