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Evidence-based treatments for female pattern hair loss: a summary of a Cochrane systematic review

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Summary

Female pattern hair loss (FPHL) or androgenic alopecia is the most common type of hair loss affecting women with reduced hair density and can have a serious psychological impact. It is characterized by progressive replacement of slow cycling terminal hair follicles by miniaturized, rapidly cycling vellus hair follicles. The frontal hair line may or may not be preserved. The aim of this review was to assess the evidence for the effectiveness and safety of the treatments available for FPHL. Searches included: Cochrane Skin Group Specialised Register, Cochrane Central Register of Controlled Clinical Trials in The Cochrane Library, MEDLINE, EMBASE, AMED, PsycINFO, LILACS and several ongoing trials registries (October 2011). Randomized controlled trials in women with FPHL were identified. Twenty-two trials, comprising 2349 participants, were included. A range of interventions was evaluated, with 10 studies examining varying concentrations of minoxidil. Pooled data from four studies indicated that a greater proportion of participants treated with minoxidil reported a moderate increase in their hair regrowth compared with placebo (relative risk 1·86, 95% confidence interval 1·42–2·43). There was no difference between the number of adverse events experienced in the twice daily minoxidil and the placebo intervention groups, except for a reported increase with minoxidil 5% twice daily. Single studies accounted for most of the other comparisons, which were assessed as either having high risk of bias and/or they did not address the prespecified outcomes for this review and provided limited evidence of either the effectiveness or safety of these interventions. Further well-designed, adequately powered randomized controlled trials investigating other treatment options are still required.

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Female pattern hair loss (FPHL) is an increasingly common clinical problem in women,[1–3] with over 21 million affected in the U.S.A. alone.[4] As its androgen-dependent nature has not been clearly established, it has been proposed that in women, the widely used term 'androgenic alopecia' should be replaced by 'FPHL'.[5,6] FPHL is characterized by progressive follicular miniaturization and the accompanying conversion of terminal follicles into vellus-like follicles.[7] The anagen phase of these vellus hair follicles is briefer and leads to production of shorter and finer hairs.[6,8] Hair shedding can vary in intensity over time, from individual to individual, and the onset of the loss of terminal hairs may precede menarche or may occur as late as the sixth decade of life.[5,9] Women who present with a reduction in hair density may also frequently exhibit thinning and widening of the area of hair loss on the central part of the scalp, which when it includes a breach of the frontal hairline is described as having a 'Christmas tree' pattern.[10,11] The frontal hairline may or may not be preserved; however, as with male pattern hair loss the degree of bitemporal recession does not necessarily correlate with the presence or severity of mid-frontal scalp hair loss.[6,12] The clinical evaluation and definition of the pattern of FPHL has traditionally relied on the Ludwig (three-point) classification;[13] however, a five-point grading scale has recently been introduced.[8,14]

This is a summary of a Cochrane systematic review that was conducted to examine the different management options and determine the most effective strategy in the treatment of FPHL.[15]

Materials and methods

We performed a systematic review of randomized controlled trials (RCTs) according to a prespecified protocol.[15]

Search strategies

We searched for relevant studies in 12 electronic databases and trial registers (Table 1) up to October 2011. We scanned the bibliographies of included studies, published reviews and articles that had cited the included studies. Attempts were made to locate unpublished and ongoing trials through correspondence with authors. No language restrictions were imposed and several studies were translated. Two review authors (E.J.v.Z. and Z.F.) independently assessed the titles and abstracts for eligible RCTs.

Inclusion criteria

RCTs that compared any type of intervention used to treat FPHL, either as a stand-alone or in combination, vs. placebo or active treatment. Studies investigating women with increased circulating androgens, whether physiological, due to polycystic ovary syndrome, or other causes were included, but we excluded studies on women with androgen-producing adrenal or ovarian tumours.

Outcome measures

Our three primary outcomes were: (i) the proportion of participants with self-rated clinically significant hair regrowth at the end of the study; (ii) change in 'quality of life' using any validated generic or disease-specific instrument, e.g. Women's Androgenetic Alopecia Quality of Life Questionnaire[16] and (iii) adverse effects: safety and tolerability and any reported adverse events. Secondary outcomes were: the proportion of participants with investigator-rated clinically significant hair regrowth at the end of the study; the mean change in total hair count from baseline to the end of the study; degree of hair shedding from baseline to the end of the study; cosmetic appearance of the hair or participant satisfaction; and change in quality (or pattern) of hair regrowth (thickness and density).

Table 1 Electronic databases and trial registers searched

Electronic databases
The Cochrane Skin Group Specialised Register
The Cochrane Central Register of Controlled Clinical Trials in The Cochrane Library
MEDLINE
EMBASE
LILACS
PsycINFO
AMED
Trial registers
The metaRegister of Controlled Trials http://www.controlled-trials.com
The U.S. National Institutes of Health Ongoing Trials Register http://www.clinicaltrials.gov
The Australian and New Zealand Clinical Trials Registry http://www.anzctr.org.au
The World Health Organization International Clinical Trials Registry platform http://www.who.int/trialsearch
The Ongoing Skin Trials Register http://www.nottingham.ac.uk/ongoingskintrials

Data extraction and synthesis

Study details and data were extracted and summarized using a structured data extraction form and disagreements were resolved by discussion. The review authors (E.J.v.Z. and Z.F.) independently assessed risk of bias in the included studies using the Cochrane Collaboration's domain-based evaluation tool as described in Chapter 8, Section 8·5, in the *Cochrane Handbook for Systematic Reviews of Interventions*.[17] We presented continuous outcomes where possible on the original scale as reported in each individual study. Dichotomous outcomes were presented as relative risk ratios. All outcomes were reported with their associated 95% confidence intervals. A meta-analysis was only carried out if there was an adequate number of studies ($n \geq 3$) investigating similar interventions and reporting data that exhibited no worse than moderate heterogeneity.[18] A fixed-effects model was used to pool the data, and a random-effects model was fitted as part of a sensitivity analysis to assess the degree of heterogeneity. We assessed clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, and the interventions. The degree of heterogeneity between the studies was assessed using the I^2 statistic. We reported heterogeneity as important if it was at least moderate to substantial ($I^2 > 60\%$).[17] If the heterogeneity could be explained by clinical reasoning and a coherent argument could be made for combining the studies these were entered into a meta-analysis whereas if the heterogeneity could not be adequately explained the data were not pooled.

Results

Description of the included studies

Results of the literature search are shown in Figure 1. Of the 334 references retrieved from the searches, only 22 studies met our inclusion criteria (see Table 2). A wide range of interventions was evaluated; 10 studies investigated minoxidil,[19–28] and four finasteride.[29–32] Two studies included cyproterone acetate in one treatment arm,[27,30] and two included flutamide.[30,31] A further 10 studies addressed other interventions: alfatradiol,[19] 0·5% octyl nicotinate and 5·0% myristyl nicotinate,[33] topical melatonin-alcohol solution,[34] topical fulvestrant solution,[35] an oral combination product of millet seed extract, L-cystine and calcium pantothenate,[36] oestrogen ointment,[37] systemic oestrogens,[38] 0·75% adenosine lotion,[39] the application of a pulsed electrostatic field,[40] and spironolactone.[31] Several of the trials compared and evaluated a number of these interventions. The treatment period ranged between 6 and 12 months. A majority of the studies included participant-assessed, in addition to investigator-assessed outcomes; however, only 11 of them evaluated 'hair regrowth', a

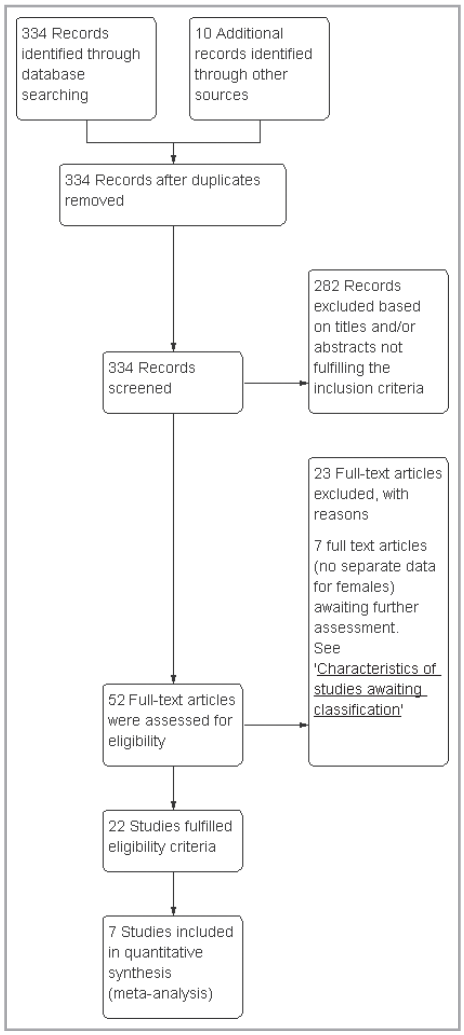

Fig 1. Search results.

primary outcome for this review.[20–26,29,30,39,40] Only one study addressed the effectiveness of interventions on quality of life,[23] while a large proportion of the trials assessed treatment-associated adverse events. The secondary outcomes were assessed in several of the studies, but the methods of measurement and the timing of the assessments were not uniform across these studies. Furthermore, some of the different methods used to measure hair growth (e.g. phototrichograms, global photography) often lacked validation.

Risk of bias of included studies

We assessed the studies for risk of bias and have reported the judgements for the individual domains in the 'risk of bias table' (see Fig. 2).

The overall risk of bias was also assessed for each study and 12 were categorized as 'high risk of bias' (plausible bias that seriously weakens confidence in the results) because one or more domain received a judgement of 'high risk'.[19–23,26,27,29,30,32,33,38] The remaining 10 studies were rated as 'unclear risk of bias' (plausible bias that raises some doubt about the result) because one or more criteria were assessed as unclear. Some of these assessments were based on the inadequate reporting of the criteria that are a prerequisite in the evaluation of methodological rigour, in terms of trial design and conduct. Concealment of the allocation sequence and blinding are key domains in the assessment of risk of bias[41] and a number of the studies in this review provided insufficient detail to enable accurate judgements. Protocol deviation, losses to follow-up with incomplete data, and subsequent per-protocol analyses were other important sources of potential bias in a number of the included studies.

Effects of interventions

See Table 3 for a summary of the key results.

Topical minoxidil

Ten studies reported data on the effectiveness of topical minoxidil.[19–28] The effectiveness and safety of minoxidil vs. placebo[21–26,28] are presented in a GRADE summary of findings table (see Table 4).[42] Neither of the two studies that compared the 2% and the 5% concentration reported any significant difference in effectiveness between either of the two concentrations of minoxidil.[20,23] In the study of Lucky *et al.*[23] minoxidil 2% twice a day was compared with minoxidil 5% twice a day and more side-effects were reported with the higher concentration. However, in the other study minoxidil 2% twice a day was compared with minoxidil 5% only once a day resulting in a similar rate of adverse events.[20] Data from two studies assessed as high risk of bias indicated that minoxidil was more effective than alfatradiol, and minoxidil combined with oral contraceptives was more effective than cyproterone acetate combined with oral contraceptives.[19,27]

Other treatment options

Some studies did not address our primary or secondary outcomes, and were not included in our systematic review.[31,34,36,38] Other studies provided limited data, and in view of this paucity of data no firm conclusions can be drawn. Octyl nicotinate (0·5%) and myristyl nicotinate (5%) might be more effective than placebo.[33] Based on the individual studies, treatment with fulvestrant,[35] adenosine,[39] pulsed electrostatic field[40] and estradiol valerate topical ointment[37] appeared to be ineffective. The investigators in one study reported that flutamide at a dose of 250 mg daily provided a modest improvement in FPHL after 1 year, whereas cyproterone acetate and finasteride were not considered to be effective.[30] Data from two studies provided no evidence to indicate that finasteride was more effective than placebo.[29,32]

Discussion

Twenty-two studies which examined 2349 participants were included. One of our key patient-preferred outcomes, 'quality

Table 2 Characteristics of included randomized controlled trials (RCTs) in the review

Study (first author)	Methods	Participants	Interventions	Outcomes
Blume-Peytavi[19]	RCT open-label Multicentre, Germany	103 women with FPHL Mean age 50·7 years (group A), 45·6 years (group B)	6 months A: Minoxidil 2% 1 mL b.i.d. B: Alfatradiol 0·025% solution 3 mL once daily	Cumulative hair thickness (mm cm^{-2}) Hair density (numbers of hairs cm^{-2}) Terminal hair density Vellus hair density Tolerability of treatment Side-effects
Blume-Peytavi[20]	RCT investigator-blind Berlin, Germany	113 women with FPHL Mean age 49·9 years	24 weeks A: Minoxidil 5% topical foam once daily B: Minoxidil 2% solution b.i.d.	Change from baseline in nonvellus target area hair count Change in nonvellus target area hair width Overall efficacy by global photographic review Adverse events Participants' assessment of product aesthetics
Carmina[30]	RCT open-label Palermo, Italy	48 hyperandrogenic women with FPHL Mean age 25 years	1 year A: Cyproterone acetate 50 mg per day day 5–15 of the cycle and ethinyl estradiol 25 μg per day day 5–25 B: Flutamide 250 mg per day C: Finasteride 5 mg per day	Hair thinning (frontal) on Ludwig scale[13] Hair growth: self-assessed questionnaire[46] Hair density: investigator-assessed; 7-point scale: greatly decreased (−3) to greatly increased (+3) Side-effects, liver function tests assessed at 3-month intervals
DeVillez[21]	RCT double-blind Multicentre, U.S.A.	308 women with FPHL Mean age 33·6 years (group A), 34·4 years (group B)	32 weeks A: Minoxidil 2% 1 mL b.i.d. B: Placebo 1 mL b.i.d.	Hair counts (photography and computer-assisted image) New hair growth: investigator and participant assessed (none, minimal, moderate, dense) Hair shedding (increased/ decreased/ unchanged) Adverse events
Draelos[33]	RCT double-blind Winston Salem, U.S.A.	60 women with FPHL Age 20–80 years	6 months A: 0·5% Octyl nicotinate and 5·0% myristyl nicotinate in vehicle, 6 drops per night to the scalp B: Vehicle, 6 drops per night to the scalp	Hair growth investigator-assessed on photograph (−1 decreased/no change/+1 increased) Appearance of hair (participant assessed) Adverse events
Fischer[34]	RCT double-blind Jena, Germany	12 women with FPHL (and 28 with diffuse alopecia) Age 20–70 years	6 months A: 0·1% Topical melatonin-alcohol solution 1 mL in the evening B: Alcohol solution 1 mL in the evening	Hair counts: frontal and occipital trichograms

Table 2 Continued.

Study (first author)	Methods	Participants	Interventions	Outcomes
Gassmueller[35]	RCT double-blind Two centres, Germany	70 postmenopausal women with FPHL Age 49–72 years	16 weeks A: 30 μL cm^{-2} Fulvestrant 70 mg mL^{-1} (0·115 mol L^{-1}) solution b.i.d. B: Vehicle b.i.d.	Hair density, TrichoScan analysis of digital images of test area Hair thickness and growth rate, TrichoScan analysis Level of systemic exposure to fulvestrant; tolerability of topical fulvestrant
Gehring[36]	RCT double-blind Karlsruhe, Germany	41 women with FPHL Mean age 38·1 years (group A), 39·2 years (group B)	6 months A: Oral combination product of millet seed extract, L-cystine and calcium pantothenate, 2 caps t.d.s. B: Vehicle, 2 caps t.d.s.	Anagen hair rate by phototrichogram
Georgala[37]	RCT Athens, Greece	75 postmenopausal women with FPHL Age 48–71 years	12–24 weeks A: Estradiol valerate topical ointment (3%) for 12 weeks B: Estradiol valerate topical ointment (3%) for 24 weeks C: Placebo vehicle for 24 weeks 15 drops per night on the affected area of the scalp for 4 weeks and then alternate nights until the end of the study period	Ratio of anagen/telogen compared with baseline Adverse events and side-effects
Jacobs[22]	RCT double-blind Multicentre, Europe	346 women with FPHL Mean age 33·1 years (group A), 34·2 years (group B)	32 weeks A: Minoxidil 2% solution 1 mL b.i.d. B: Placebo 1 mL b.i.d.	Hair counts (nonvellus); photography, computer-assisted image New hair growth (investigator and participant assessed) rated minimal/moderate/dense Safety evaluation (ECG/serum chemical tests/urinalysis)
Lucky[23]	RCT double-blind Multicentre, U.S.A.	381 women Age 18–49 years	48 weeks A: Minoxidil 2% solution 1 mL b.i.d. B: Minoxidil 5% solution 1 mL b.i.d. C: Placebo lotion b.i.d.	Hair counts (nonvellus) Hair growth/scalp coverage (participant assessed) Hair growth/scalp coverage (investigator assessed) Participant assessed: 12-item questionnaire: quality of life (6), global benefit (6). i.e. hair growth, hair styling measures Safety evaluation
Minozzi[38]	RCT Rome, Italy	63 postmenopausal women with FPHL Age 52–63 years	12 months A: Ethinyl estradiol 0·02 mg per day day 1–25 of each month, MPA 10 mg daily added for last 10 days of oestrogen administration B: Transdermal estradiol 0·05 mg per day and MPA for last 10 days of oestrogen administration C: Ethinyl estradiol 0·02 mg per day day 1–25 of each month. Cyproterone acetate 12·5 mg daily added for first 10 days of oestrogen administration	Hormonal assays Trichogram (with microscope)

Table 2 Continued.

Study (first author)	Methods	Participants	Interventions	Outcomes
Olsen[24]	RCT double-blind Durham, U.S.A.	30 women with FPHL Mean age 36·0 years (group A), 38·9 years (group B)	32 weeks A: Minoxidil 2% solution 1 mL b.i.d. B: Placebo 1 mL b.i.d.	Hair counts at target area (frontoparietal tattooed) macrophotography assessed Regrowth: subjective assessment (investigator/participant) rated none/ minimal/ moderate/ dense regrowth) Adverse effects
Oura[39]	RCT double-blind Tokushima, Japan	30 women with FPHL Mean age 38·9 years	12 months A: Adenosine (0·75%) solution 3 mL b.i.d. B: Vehicle 3 mL b.i.d.	Hair loss (dermatologist assessed): standardized photographic techniques (6-point scale: 1 = no hair loss, 6 = detectable hair loss)[47] Improvement in hair loss (investigator assessed): standardized photography Phototrichograms Self-assessments: 7-item questionnaire[46]
Policarpi[40]	RCT Florence, Italy	6 women with FPHL (and 24 men with AGA) Mean age 29·1 years	36 weeks A: Pulsed electrostatic field applied 12 min session per week B: Sham treatment	Hair count (anagen) standardized photographic technique Self-assessment: clinical condition (4-point scale: 0 = worse, 3 = significantly improved) Investigator assessed satisfaction with clinical condition (4-point scale)
Price[25]	RCT double-blind Two centres, U.S.A.	9 women with FPHL Age 22–41 years	40 weeks A: Minoxidil 2% solution 1 mL b.i.d. B: Placebo 1 mL b.i.d.	Clipped samples: hair weight; hair count; hair width/length
Price[29]	RCT double-blind Multicentre, U.S.A.	137 women Mean age 53 years	12 months A: Oral finasteride 1 mg per day B: Placebo	Hair counts; computer-assisted scans of macrophotographs of clipped hair in a defined (dot tattoo) circular target area (1 cm^2) Hair growth participant/self-assessed; modified version of a validated questionnaire[46] Hair growth investigator assessed; standardized 7-point scale (−3 = greatly decreased to +3 = greatly increased) Scalp biopsies Laboratory tests
Tsuboi[26]	RCT double-blind Multicentre, Japan	280 women with FPHL Mean age 56·3 years (group A), 57·2 years (group B)	24 weeks A: Minoxidil 1% solution 1 mL b.i.d. B: Placebo 1 mL b.i.d.	Hair counts: photography/microscopy assessed Hair growth; investigator assessed photographic comparison (5-point scale: 1 = markedly improved to 5 = worsened) Hair growth; participant assessed (5-point scale) Hair loss; participant-assessed (3-point scale: 1 = decreased hair loss, 3 = increased hair loss) Adverse events

Table 2 Continued.

Study (first author)	Methods	Participants	Interventions	Outcomes
Ukşal[31]	RCT Kayseri, Turkey	Number unclear, age unclear (poster)	3 months A: Oral spironolactone 100 mg per day B: Oral flutamide 125 mg per day C: Oral finasteride 2·5 mg per day	Not stated
Vexiau[27]	RCT Paris, France	66 women with FPHL (including women with hyperandrogenic profile) Mean age 26·4 years	12 months A: Minoxidil 2% 1 mL b.i.d. in association with combined oral contraceptive: ethinyl estradiol 30 μg per day and gestodene 75 μg per day for 21 of 28 days B: Cyproterone acetate 50 mg per day for 20 of 28 days, plus a combination of ethinyl estradiol 35 μg per day and cyproterone acetate 2 mg per day for 21 of 28 days	Number of hairs > 40 μm in diameter measured Phototrichogram Total number of hairs Number of hairs in the anagen and telogen phases Patient assessment (VAS) cosmetic effectiveness of treatment
Whiting[28]	RCT double-blind Two centres, Texas, U.S.A.	33 women with FPHL Mean age 34 years	32 weeks A: Minoxidil 2% solution 1 mL b.i.d. B: Placebo 1 mL b.i.d.	Hair counts: macrophotograph predefined tattooed area and count with Quantimet 920 Image Analyzer Overall growth: global photograph of affected area Regrowth: investigator and participant assessed (subjective) Hair shedding participant assessed between visits
Whiting[32]	RCT Multicentre, U.S.A.	137 postmenopausal women with FPHL Age 41–60 years	12 months A: Finasteride 1 mg per day B: Placebo	Scalp biopsy

b.i.d., twice daily; ECG, electrocardiography; FPHL, female pattern hair loss; MPA, medroxyprogesterone acetate; t.d.s., three times daily; VAS, visual analogue scale.

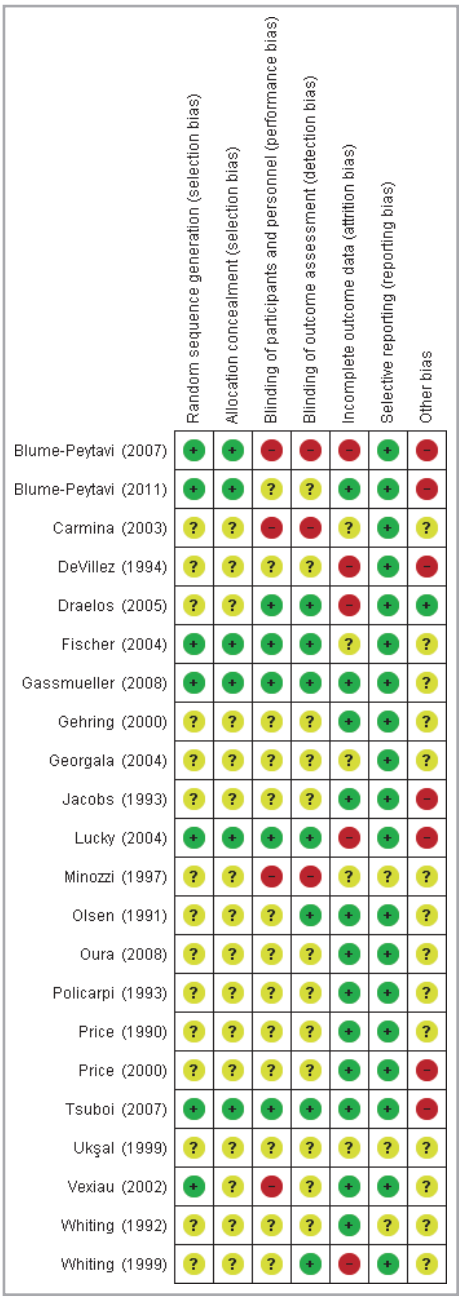

Fig 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. +, 'low risk of bias'; ?, 'unclear risk of bias'; −, 'high risk of bias'.

of life', was assessed in only one of the studies.[23] The majority of studies focused on change in total (nonvellus) hair count which although this may provide a quantifiable, objective and more readily intelligible outcome, is considered to be physician preferred rather than an outcome addressing patients' preferences.

FPHL can be distressing and is known to have an impact on quality of life, and thus the importance of assessing the effectiveness of interventions targeted at improving this key outcome should not be underestimated.[43] Pooling of data was only feasible for a few of the outcomes and was confined to those that evaluated the effectiveness of minoxidil compared with placebo (see Table 4).

Based on the findings of this review the only intervention that appeared to demonstrate a measure of effectiveness was minoxidil. The 2% concentration illustrated a good safety profile, and more undesirable side-effects, such as hypertrichosis and increased hair growth on other areas than the scalp, were associated with the 5% concentration used twice a day,[23] but not with minoxidil 5% used only once a day.[20] However, doses in excess of 60 mg a day may lead to an increase in the number of adverse effects and with application of minoxidil 5% twice a day (100 mg) that threshold is substantially exceeded.

Most interventions were evaluated in single studies, and none of the studies addressed more than a very limited number of our outcomes, illustrating a lack in the overall completeness of the evidence. Several ongoing studies were identified which may eventually help to fill in some of the gaps in the evidence for the other interventions, e.g. spironolactone and finasteride.[15]

Although study design in the included studies appeared to have been at best adequate, our study-level assessments of the risk of bias for a number of the domains in several of these studies revealed some of the limitations in their implementation (see Fig. 2). There was considerable variation in how well the studies were reported, and in particular the methods used to generate the sequence, to conceal the allocation, and the measures taken to blind investigators and participants. These factors, compounded with unsuccessful attempts to contact many of the investigators for additional information, created difficulties in making accurate assessments of the risk of bias in almost half of the included studies. In many instances, the key outcomes that were assessed in the included studies provided limited data, much of which could not be pooled except for minoxidil, and, consequently, did not allow any wider assessment or comparison of the effects of the interventions across the studies. The quality of data reporting in the included studies was very variable across the studies, and, in several it was unclear to what extent the impact of industry sponsorship may have had on the direction and completeness of the results. Unfortunately, previous studies which examined spironolactone, cyproterone acetate, finasteride and flutamide were generally nonrandomized controlled trials and were therefore not included in our Cochrane review.

Patient-relevant primary outcomes are a prerequisite for informing evidence-based decision making, but the importance of patient-reported outcomes and specifically those used in evaluating the impact of interventions on quality of life, and which are of direct relevance to patients, appears to have been underestimated by the investigators in the majority of the included studies.

The more recently published 'Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and men' was commissioned by the European Dermatology Forum to evaluate the 'efficacy of the currently available therapeutic

Table 3 Summary of results of included studies

Study (first author)	Interventions	Summary outcomes	Comments
Blume-Peytavi[19]	A: Minoxidil 2% b.i.d. B: Alfatradiol 0·025% once daily	Mean change in cumulative hair thickness: group A 1·8 (SD 2·3) mm cm^{-2} compared with group B −0·5 (SD 2·5) mm cm^{-2} ($P > 0·05$) Increase in hair density: group A 15·3 hairs cm^{-2} (SD 29·0) ($P = 0·003$) compared with group B −7·8 hairs cm^{-2} (SD 24·6) ($P > 0·05$) No adverse events were reported	Significant losses to follow up are likely to have had an impact on the precision although not the direction of the effect estimate
Blume-Peytavi[20]	A: Minoxidil 5% topical foam once daily B: Minoxidil 2% b.i.d.	44% of group A vs. 39% of group B experienced moderate to greatly increased hair regrowth (RR 1·12, 95% CI 0·72–1·73) 51/57 of group A compared with 43/56 in group B reported adverse events (RR 1·17, 95% CI 0·98–1·38) The investigators assessed 12/57 in group A to have moderate to greatly increased hair growth compared with 14/56 in group B (RR 0·84, 95% CI 0·43–1·66) The mean difference in total hair count between group A and group B was −3·50 (95% CI −10·55–3·55) Almost three-quarters of those in group A were more satisfied with the appearance of their hair at the end of treatment compared with more than half of those in group B No statistically significant difference in the nonvellus cumulative target area hair width (mm cm^{-2}) between the two groups	
Carmina[30]	A: Cyproterone acetate and ethinyl estradiol B: Flutamide C: Finasteride	2/12 in group A reported improvement in hair growth compared with 3/12 in group B and 1/12 in group C No adverse events were reported Slowing down hair loss: 3/12 in group A, 8/12 in group B vs. 1/12 in group C	
DeVillez[21]	A: Minoxidil 2% b.i.d. B: Placebo b.i.d.	26/157 of group A vs. 9/151 of group B reported moderate increase in hair growth (RR 2·78, 95% CI 1·35–5·73) Adverse events were 'similar' in both groups Increase in total hair count in group A when compared with group B was 12·0 (95% CI 6·34–17·66)	Large number of drop-outs (17%), incomplete outcome data
Draelos[33]	A: 0·5% Octyl nicotinate and 5·0% myristyl nicotinate in vehicle B: Vehicle	Data for adverse events were not reported separately The investigators reported that 22/40 of group A had an increase in hair fullness vs. 4/20 of group B (RR 2·75, 95% CI 1·10–6·90) No statistically significant difference between the groups regarding assessments of the appearance of their hair	Incomplete outcome data were not adequately addressed, timing of and reasons for withdrawal unreported, and with substantial differences between the two groups
Fischer[34]	A: 0·1% Topical melatonin-alcohol solution B: Alcohol solution	None of our primary or secondary outcomes was assessed	
Gassmueller[35]	A: Fulvestrant 70 mg mL^{-1} solution b.i.d. B: Vehicle b.i.d.	Adverse events: 10/34 in group A vs. 16/36 in group B (RR 0·66, 95% CI 0·35–1·25) No statistically significant differences in terms of percentage change from baseline in cumulative hair thickness, nor in hair density	Limited outcomes data for this comparison

Table 3 Continued.

Study (first author)	Interventions	Summary outcomes	Comments
Gehring[36]	A: Oral combination product of millet seed extract, L-cystine and calcium pantothenate B: Vehicle caps	None of our primary or secondary outcomes was assessed	
Georgala[37]	A: Estradiol valerate topical ointment (3%) for 12 weeks B: Estradiol valerate topical ointment (3%) for 24 weeks C: Placebo vehicle for 24 weeks	Adverse events: 2/25 in group A reported mild pruritus on the scalp compared with 4/25 in group B and 2/25 in group C. In group C 2 participants experienced postmenopausal uterine bleeding resulting in their withdrawal from the study	Minimal data for this comparison
Jacobs[22]	A: Minoxidil 2% b.i.d. B: Placebo b.i.d.	Participant-rated clinically significant hair regrowth: 39/176 of group A compared with 17/170 of group B (RR 2·22, 95% CI 1·31–3·76) Adverse events: 2/176 of group A vs. 0/170 of group B (RR 4·83, 95% CI 0·23–99·89) According to the investigators 19/176 of group A compared with 7/170 of group B had a moderate increase in hair regrowth (RR 2·62, 95% CI 1·13–6·08) Increase in total hair count in group A when compared with group B was 14·00 (95% CI 9·07–18·93)	
Lucky[23]	A: Minoxidil 2% b.i.d. B: Minoxidil 5% b.i.d. C: Placebo b.i.d.	The investigators reported that there was no statistically significant difference in impact of hair loss on quality of life between the two active intervention groups. However, there was a statistically significant difference between group A and group B when compared with placebo Adverse events: 10/154 of the participants in group A compared with 22/153 in group B and 3/74 in group C Mean difference of −3·80 in total hair count between the minoxidil 2% and 5% group (95% CI −9·21–11·61). Comparing group A with group C there was a mean difference of 11·30 (95% CI 4·78–17·82) and between group B and group C a mean difference of 15·10 (95% CI 7·96–22·24) No statistically significant difference in hair density between group A and group B. However, there was a statistically significant difference between the two active treatment groups and the placebo group	Although the scores on impact on quality of life were reported without standard deviations and as statistically significant by the investigators, the mean differences between intervention groups were marginal and can be considered not clinically important Losses to follow-up/withdrawals were substantial (> 30%) in all treatment groups
Minozzi[38]	A: Ethinyl estradiol 0·02 mg per day and MPA 10 mg per day B: Transdermal estradiol 0·05 mg per day and MPA C: Ethinyl estradiol 0·02 mg per day and cyproterone acetate 12·5 mg per day	None of our primary or secondary outcomes was assessed	

Table 3 Continued.

Study (first author)	Interventions	Summary outcomes	Comments
Olsen[24]	A: Minoxidil 2% b.i.d. B: Placebo b.i.d.	Participant-rated clinically significant hair regrowth: 6/15 of group A compared with 6/15 of group B (RR 1·00, 95% CI 0·42–2·40) Adverse events: 3/15 of group A vs. 4/15 of group B (RR 0·75, 95% CI 0·20–2·79) According to the investigators 6/15 of group A compared with 1/15 of group B had a moderate increase in hair regrowth (RR 6·00, 95% CI 0·82–44·00) Increase in total hair count in group A when compared with group B was 29·50 (95% CI 10·98–48·02)	
Oura[39]	A: Adenosine (0·75%) b.i.d. B: Vehicle b.i.d.	Assessments of improvement in hair growth rated by a dermatologist, the investigator and the participants were in agreement that adenosine was not effective compared with placebo	
Policarpi[40]	A: Pulsed electrostatic field B: Sham treatment	2/4 in group A showed a significant improvement compared with 0/2 in group B The investigator-rated assessments indicated that there was no clinically significant hair growth observed in the participants in both treatment arms	Poorly reported trial provided independent patient data for the six female participants
Price[25]	A: Minoxidil 2% b.i.d. B: Placebo b.i.d.	Increase in total hair count in group A when compared with group B was 42·00 (95% CI 15·71–68·29)	
Price[29]	A: Oral finasteride 1 mg per day B: Placebo	30/67 of the participants in group A considered themselves improved vs. 33/70 in group B (RR 0·95, 95% CI 0·66–1·37) Adverse events: 53/67 in group A vs. 55/70 in group B (RR 1·03, 95% CI 0·45–2·34) The investigators reported that 10/67 participants in group A showed a moderate increase vs. 13/70 in group B (RR 0·77, 95% CI 0·31–1·90) Degree of hair loss by hair count, with a mean decrease from baseline in hair count of 8·7 hairs in group A vs. 6·6 in group B	Although the investigators provided no data they reported that there was no statistically significant difference in the slowing down of hair loss nor the cosmetic appearance/satisfaction between the two groups at the end of the study
Tsuboi[26]	A: Minoxidil 1% b.i.d. B: Placebo b.i.d.	Participant-rated clinically significant hair regrowth: 50/140 of group A compared with 32/140 of group B (RR 1·56, 95% CI 1·07–2·28) Adverse events: 19/140 of group A vs. 17/140 of group B (RR 1·12, 95% CI 0·61–2·06) According to the investigators 40/140 of group A compared with 16/140 of group B had a moderate increase in hair regrowth (RR 2·50, 95% CI 1·47–4·25) Increase in total hair count in group A when compared with group B was 12·30 (95% CI 7·87–16·73)	

Table 3 Continued.

Study (first author)	Interventions	Summary outcomes	Comments
Ukşal[31]	A: Spironolactone B: Flutamide C: Finasteride	None of our primary or secondary outcomes was assessed	Poster, limited data were reported
Vexiau[27]	A: Minoxidil 2% 1 mL b.i.d. in association with combined oral contraceptive consisting of ethinyl estradiol 30 μg per day and gestodene 75 μg per day for 21 of 28 days B: Cyproterone acetate 50 mg per day for 20 of 28 days, plus a combination of ethinyl estradiol 35 μg per day and cyproterone acetate 2 mg per day for 21 of 28 days	3 participants in group A reported pruritus and 1 reported weight gain, and 1 participant in group B reported weight gain The mean difference in total number of hairs per 0·36 cm^2 between group A and group B was 7·90 (95% CI 3·70–12·10)	
Whiting[28]	A: Minoxidil 2% solution 1 mL b.i.d. B: Placebo 1 mL b.i.d.	Authors state that no serious adverse events had occurred Increase in total hair count in group A when compared with group B was 8·00 (95% CI −9·64–25·64)	
Whiting[32]	A: Finasteride 1 mg per day B: Placebo	Increase of 0·2 in change from baseline in total hair count of terminal hairs in group A vs. 1·1 in group B	

b.i.d., twice daily; CI, confidence interval; RR, relative risk; MPA, medroxyprogesterone acetate.

Table 4 Summary of findings of minoxidil vs. placebo for female pattern hair loss[21–26,28]

Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Minoxidil			
The proportion of participants with self-rated clinically significant hair regrowth at the end of the study 3- and 5-point scales[b]	Study population 134 per 1000	250 per 1000 (191–327)	RR 1·86 (1·42–2·43)	964 (4 studies)	++–– low[c,d]
Follow-up: 24–32 weeks	Moderate				
Change in 'quality of life' using any validated and recognized generic or disease-specific instrument[e] – not reported	See comment	See comment	Not estimable[e]	–	See comment
Adverse effects: safety and tolerability and any reported adverse events 1% minoxidil	Study population 121 per 1000	136 per 1000 (74–250)	RR 1·12 (0·61–2·06)	280 (1 study)	+++– moderate[f]
Laboratory values, blood pressure, participant-reported adverse effects at recall	Moderate				
Follow-up: 24 weeks					
Adverse effects: safety and tolerability and any reported adverse events 2% minoxidil	Study population 27 per 1000	38 per 1000 (16–88)	RR 1·4 (0·6–3·27)	604 (3 studies)	+++– moderate[f]
Structured interview, physical examination and laboratory investigations	Moderate				
Follow-up: 32–48 weeks					
Adverse effects: safety and tolerability and any reported adverse events 5% minoxidil	Study population 41 per 1000	144 per 1000 (45–465)	RR 3·55 (1·1–11·47)	227 (1 study)	+++– moderate[f]
Structured interview, physical examination and laboratory investigations	Moderate				
Follow-up: 48 weeks					
Change in total hair count from baseline to the end of the study Hair counts in 1–1·5 cm^2 area. Scale from −3·25 to 50·14	The mean change in total hair count from baseline to the end of the study ranged across control groups from −3·25 to 20·64	The mean change in total hair count from baseline to the end of the study in the intervention groups was 13·28 higher (10·89–15·68 higher)		1166 (7 studies[g])	++–– low[h]
Follow-up: 24–48 weeks					

CI, confidence interval; RR, risk ratio. [a]The basis for the assumed risk (e.g. the median control group risk across studies) is provided below. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence are as follows. High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: we are very uncertain about the estimate. [b]3-point scale: none, mild, moderate; 5-point scale: markedly improved, moderately improved, slightly improved, unchanged, worsened. [c]3/4 studies key domains of risk of bias, i.e. sequence generation, allocation concealment and blinding judged 'unclear'. Tsuboi *et al.*[26] 'low risk'. [d]Olsen[24] small study, no difference between two treatment arms; other larger studies show treatment effect. [e]Lucky *et al.*[23] quality of life assessed six-item questionnaire; 100 mm visual analogue scale rated 0, negative to 100, positive. Unreported if questionnaire piloted tested or validated. [f]Wide CI. [g]Lucky *et al.*[23] comparisons 2% minoxidil vs. placebo; 5% minoxidil vs. placebo. [h]Price and Menefee[25] outlier, small sample size ($n = 8$). Possible publication bias; single participant with large treatment effect; result may be due to natural sampling variation.

options'.[44] Although its development relied heavily on a formal consensus process negotiated between members of the guideline group and was therefore deemed reasonably transparent, we are in disagreement over the robustness of the methodological approach used in its development. Lack of clarity in the process and ultimately its reproducibility was illustrated by the incomplete reporting of some of the important steps taken in: study assessment; handling of missing trial data; analysis and interpretation of results; and summary of the adverse events.

We recognize an important area of discord with the method of grading of evidence for this guideline, which was based on study design and 'summarised in a level of evidence' and combined study design with a quality measure described by the developers as 'mainly consistent results'. However, these consistencies or inconsistencies, or indeed how they were defined or assessed in the individual studies, were unreported. It remains unclear if these referred to factors which were a potential source of bias and, as distinct from this systematic review, no risk of bias assessments were undertaken and nothing was reported by the guideline developers. In making their study level assessments of evidence, the S3 guideline developers did not appear to have taken into consideration the conceptual differences between methodological quality and reporting quality. Thus the 'level of evidence' in the guideline was based on the methodological quality of the individual trial as reported, with no clear indication if the developers had attempted to contact investigators to clarify missing trial details and data, which would have enabled more robust and exhaustive assessments of risk of bias to be carried out. The strength of clinical recommendations in this S3 guideline was based on the level of evidence and several other factors, none of which was clearly defined nor appeared to correspond to the widely recognized GRADE approach to developing and presenting recommendations for management of patients.[45] In contrast, we used this method in this review to examine and categorize the quality level of a body of evidence and thus indicate our confidence in the effect estimate for minoxidil in particular (see Table 4).

Therefore, while we concur with the general conclusions reached in this S3 guideline in terms of direction of treatment effect, we express a level of disagreement with the order of magnitude as reported, and specifically where it underpins the clinical recommendations for minoxidil.

In conclusion, from this Cochrane review, evidence of treatment effect could only be demonstrated for minoxidil. Minoxidil 2% topical solution twice daily appears to be effective and safe, and the minoxidil 5% concentration used once daily may be as effective as the 2% used twice daily, a factor which is likely to result in improved compliance. In view of these findings further research is required, and in particular on direct comparisons of minoxidil 5% applied once a day vs. minoxidil 2% twice daily. However, it should be noted that the higher concentration (5%) is only registered for therapeutic management of FPHL in a small number of countries. It is widely perceived that minoxidil 2% is more effective than the 1% concentration and this is reflected in the fact that the 2% concentration is most frequently registered worldwide for FPHL. However, the results from one study included in this review indicate that the 2% does not appear any more effective than the 1%, and is associated with a greater number of adverse events.

There is an urgent need for high-quality, well-designed, and rigorously reported studies of other widely used treatments such as spironolactone, finasteride, cyproterone acetate, and laser comb therapy.

There was wide variability in not only the conduct but also in the quality of reporting of many of the trials. Therefore a major area for improvement would be in the standardization of outcome reporting in any future research. The use of proprietary severity scales and nonstandardized scales significantly hampered our ability to combine study results for a meta-analysis. Outcomes sought and collected in future trials should be primarily based on a standardized scale of the participant's assessment of the treatment efficacy and should also have a greater emphasis on changes in quality of life as a result of the interventions. Standardized and uniform scales should be developed and used for physicians' assessments, and these should reliably reflect the proportion of participants with investigator-rated clinically significant hair regrowth and mean change in total hair count from baseline to the end of the study. Follow-up studies addressing the sustainability of hair regrowth after discontinuation of treatment should be taken into account as they constitute an important outcome for participants.

Future RCTs must be well-designed, well-conducted, and adequately delivered with subsequent reporting, including high-quality descriptions of all aspects of methodology. Rigorous reporting needs to conform to the Consolidated Standards of Reporting Trials (CONSORT) statement and this will enable appraisal and interpretation of results, and accurate judgements to be made about the risk of bias, and the overall quality of the evidence.

Clinical decision making on the choice of intervention for FPHL should be based on high-level evidence if it is available, but in the absence of such evidence for any other specific intervention these decisions should continue to be guided by clinical experience and patients' individual characteristics and preferences until such time as further evidence for these other interventions becomes available.

In view of the fact that there may be a delay before any treatment effect can be noticed, and as most of the available treatments fail to achieve the desired end result, cosmetic aids and hair transplant surgery need to be included in the decision-making process. Furthermore, physicians should also try to address the psychosocial impact, coping mechanisms and quality of life-related issues when treating women with FPHL.

What's already known about this topic?

- Female pattern hair loss or androgenic alopecia is the most common type of hair loss affecting women with reduced hair density and can have a significant negative psychological impact.

- Various treatment options are available but it is unclear which are the most effective.

What does this study add?

- Minoxidil appears to be effective and safe for the treatment of female pattern hair loss.
- Minoxidil 2% administered twice a day may be as effective and safe as minoxidil 5% once a day, but further studies are warranted.
- There is a lack of evidence for the effectiveness of some of the widely used treatments such as spironolactone, cyproterone acetate, finasteride and laser comb therapy.

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