Approximately 80% of women are affected by the presence of excessive hair growth in a “male-like” pattern. Excessive facial hair in particular can be a source of distress to such women and can lead to psychological problems such as anxiety, depression and a reduced quality of life. Current cosmetic methods of hair removal include shaving, depilatories, waxing, plucking, laser, intense pulsed light (IPL) and electrolysis. A topical treatment cream such as eflornithine 11.5% can slow hair growth and thus reduce the frequency of the need for hair removal. This treatment can be used effectively in conjunction with hair removal methods.

Introduction

Hirsutism is a highly distressing and relatively common problem in females and is often an indicator of endocrine imbalance. Based upon the discussions which took place at a meeting of the Endocrinology and Diabetes and Dermatology Sections of the Royal Society of Medicine (London, October 2004), this paper aims to provide guidance as to the clinical management of this condition alongside information on the background to hirsutism, its prevalence and aetiology.

Hirsutism is defined as the presence of unwanted terminal (coarse) hairs in females in a pattern more typically seen in adult males. This is in contrast to hypertrichosis, which is independent of androgen influence and is manifested by the superfluous and uniform growth of non terminal (vellus) hair over the body; particularly in non sexual areas. Hair growth in hypertrichosis is abnormal for the age, sex, or race of an individual, or for a particular area of the body. It can occur as a result of treatment with drugs (e.g. minoxidil, cyclosporine) or as a consequence of metabolic or nutritional disturbances such as anorexia nervosa, porphyria or hypothyroidism. Approximately eight percent of women are affected by the presence of excessive hair growth in a male-like pattern. Excessive facial hair in particular can be a source of psychological distress in women and can lead to problems such as anxiety, depression and a reduced quality of life. It is believed to affect between 5 and 15% of women, although this figure is likely to be an underestimation of the exact prevalence. Lesser degrees of facial hair growth, while less often attributable to endocrine disturbance, can also prove a source of distress to women.

Current cosmetic methods of hair removal include shaving, depilatories, waxing, plucking, laser, intense pulsed light (IPL) and electrical depilation. A treatment that can slow hair growth and thus reduce the frequency of the need for hair removal would be of benefit to women affected by excessive facial hair.

* The material published here draws upon the unpublished proceedings of Hirsutism – a joint meeting of the Endocrinology and Diabetes and Dermatology Sections, Royal Society of Medicine, London, 13 October 2004
Aetiology of female hirsutism

Hirsutism is usually the result of an underlying follicular or central endocrine abnormality. Elevated secretion of androgens, increased bioavailability of testosterone and increased sensitivity of hair follicles to androgens all contribute to excess female body hair growth. The most common ‘central’ cause of this condition is polycystic ovary syndrome (PCOS), which accounts for between 70 and 90% of all cases.

Idiopathic hirsutism accounts for between 6 and 17% of cases. Women with idiopathic hirsutism have normal menstruation and serum androgen levels within the normal range.

Rarely, conditions such as non-classical (late onset) congenital adrenal hyperplasia, Cushing’s disease and androgen-secreting tumours of the ovary or adrenal gland are found to cause hirsutism: such patients present with varying degrees of virilisation (temporal hair recession, deepening of the voice, clitoromegaly). Hirsutism, particularly when rapidly progressing, should be carefully assessed to exclude these endocrine possibilities, particularly tumours.

There is a strong genetic component to hirsutism, primarily because the underlying endocrine disorders (e.g. PCOS) and the factors regulating the development of hair growth possess genetic factors themselves.

PCOS and hirsutism

PCOS is characterised by the formation of follicular cysts detected by ultrasound. PCOS is the combination of polycystic ovaries and one or more characteristic features (see Table 1).

The diagnosis of PCOS is frequently one of exclusion. This means that it is a disorder attributed to patients with evidence of ovulatory dysfunction supported by either biochemical or clinical evidence of hyperandrogenism after the presence of similar disorders (such as non-classic adrenal hyperplasia, hyperandrogenism, insulin resistance and acanthosis nigricans or HA-IR-AN, androgen secreting neoplasms, or thyroid or prolactin dysfunctions) have been eliminated. PCOS is a wide-spectrum disorder; those affected ranging from women with regular cycles who have hirsutism to those who are anovulatory. In PCOS, the source of the excess androgens is the ovary theca cells which produce an excess amount of androstendione, a direct precursor of testosterone.

Laboratory analyses will show a decreased plasma concentration of follicle-stimulating hormone (FSH) and a raised plasma concentration of luteinising hormone (LH).

Hirsutism in PCOS is typically gradual in onset and patients may also present with greasiness of the skin, some vertex hair loss (androgenetic alopecia) and acne. Insulin resistance can also be associated with hirsutism, and obesity may exacerbate the condition, probably by lowering serum sex hormone-binding globulin (SHBG) concentrations, thereby increasing the percentage of unbound testosterone. In the obese, a relatively small reduction in weight can help hirsutism in the long term by increasing SHBG and therefore reducing free androgen levels.

Insulin also directly stimulates theca cells in the ovary. It should be noted that obese women with PCOS are at an elevated risk of developing diabetes and consequently need to be encouraged to lose weight, this can dramatically reduce the excess facial hair. In cases of mild hirsutism, accompanied by acne and regular ovulation, a hair removal strategy in combination with appropriate endocrine treatment is recommended. Women with severe hirsutism in PCOS are likely to see a worsening of their condition at menopause due to secretion of more ovarian androgens at this time.

The role of androgens in hair growth

Androgens play an important role in hair growth, being responsible for the conversion of vellus hairs into terminal ones (secondary sexual hair) and also, paradoxically for vertex scalp hair loss (androgenetic).

The control of androgens in beard growth was recorded in the 1950s by Hamilton and colleagues. They studied men who had been castrated at different ages and found that those castrated after 30 years of age still grew beards while those castrated in their early 20s or younger had little beard growth, showing that obliterating androgens once terminal hair growth is fully established does not significantly alter its growth.

Androgen-dependent hair growth is site dependent and a specific response of the hair follicle to androgens. Treatments which destroy hair follicles destroy the stem cell population.

In contrast, hormonal therapies for female hirsutism target androgen action by suppressing its synthesis directly, lowering insulin resistance and, where appropriate, blocking the peripheral androgen receptivity, or inhibiting 5-alpha reductase conversion of testosterone to dihydrotestosterone.

Table 1. Typical symptoms and signs of PCOS

| Amenorrhea or dysfunctional uterine bleeding |
| Hirsutism |
| Obesity |
| Infertility |
| Irregular menstrual cycle |
| Acne |
Assessment of hirsutism

Detailed clinical and endocrine evaluation is essential to establish the cause of the condition in every case. The diagnosis of hirsutism is usually fairly straightforward once other causes of increased hair growth (hypertrichosis) have been eliminated.

As discussed previously, PCOS can be established by testing for biochemical abnormalities such as an increased LH:FSH ratio, serum LH in excess of 10IU/L, a lowered SHBG and a serum testosterone at or above the upper limit of normal.

Visual assessment of the degree of excess terminal hair can be made using the Ferriman–Gallwey scale. The original scale scored hair density on a scale of 1–4 at 11 androgen-sensitive body sites; however this has been modified to include nine body sites because arms and legs are currently not considered to be androgen-sensitive sites.

Mild cases of hirsutism without a sudden progressive increase in hair growth do not need more than serum testosterone to support clinical assessment; some authorities also recommend ovarian ultrasound. Moderate cases with or without normal ovulatory cycles should always be investigated by measuring serum testosterone, LH and FSH and performing ultrasound. However, severe hirsutism of sudden onset can potentially indicate a serious problem and warrants more extensive endocrine investigation.

Management of hirsutism

Treatment choices ultimately depend upon the underlying cause. Pharmacological treatments include metformin, cyproterone acetate, flutamide, spironolactone and finasteride. Physical and cosmetic therapy (such as shaving, electrolysis, laser, IPL etc.) is necessary alongside pharmaceutical treatments.

Metformin is an antidiabetic treatment, not indicated for the treatment of female hirsutism alone. It is an antihyperglycaemic agent which works by helping the body to regulate blood sugar more effectively. It is thought that by reducing the levels of circulating insulin in the body, metformin decreases free androgen concentrations and thereby improves hirsutism as a result. The usual dose in hirsutism is 1500 mg/day. Trial work has revealed that metformin can be effective for the treatment of hirsutism caused by PCOS. Research has also found that metformin reduces circulating testosterone in women with PCOS, and furthermore that extended use can lead to improvements in body mass index and help regulate the menstrual cycle. Metformin can be prescribed for women with PCOS whose hirsutism is thought to arise from insulin resistance, a condition where the ovaries produce excess androgens. One rare potential complication of metformin treatment is lactic acidosis. Metformin treatment is also associated with gastrointestinal disorders.

Depending upon the particular case and cause of hirsutism, hormonal therapy may be advocated with products containing cyproterone acetate (CPA), a progestogen which possesses anti-androgenic properties. The dosage in hirsutism is usually within the range of 50–100 mg daily. CPA is often combined with a synthetic oestrogen such as ethinyloestradiol (e.g. co-cyprindiol 2000/35; cyproterone acetate 2 mg, ethinyloestradiol 35 µg). CPA blocks androgen receptors and reduces androgen synthesis by inhibiting androgen-synthesising enzymes. In addition to its potential to improve hirsutism, co-cyprindiol is also a contraceptive and it can help ameliorate acne. A prospective randomised trial by Beigi et al. found a significant reduction in modified Ferriman–Gallwey scores versus baseline when patients were treated with 20 mg/day on days 5–25. It can take up to a year of treatment with co-cyprindiol before the desired hair loss is achieved and treatment may need to be continued for as long as the patient wishes to be treated for hirsutism. There are risks associated with taking a prescription-only hormonal treatment including hypertension, venous thromboembolism, diabetes mellitus, hypercholesterolaemia and endometrial cancer. Patients should be advised of these risks, particularly since patients with underlying PCOS are at an increased risk of cardiovascular disease.

CPA can also be used under hospital supervision for the treatment of hirsutism. In cases where co-cyprindiol 2000/35 alone is not effective, CPA can be added on days 1–10 of the 21-day Co-cyprindiol 2000/35 dosing cycle to give a greater degree of anti-androgen control. Despite the drug having been available since the 1960s, the evidence from dose ranging studies is still equivocal. A study by Barth et al. found no significant differences in clinical measures of facial hair growth between co-cyprindiol 2000/35, co-cyprindiol 2000/35 plus 20 mg CPA and co-cyprindiol 2000/35 plus 100 mg CPA. This indicates that 2 mg CPA is as effective as higher doses in the treatment of hirsutism. To date there is no conclusive evidence to support the addition in clinical practice of higher doses of CPA (50–100 mg) to co-cyprindiol 2000/35 treatment as this does not confer any additional clinical benefit in the treatment of hirsutism. Patients should be made aware that it can take up to a year of treatment before the full benefits are seen. The hair invariably returns rapidly when treatment is stopped meaning that regular therapy cycles are required to control hirsutism.

Treatment with a low-dose oestro-progestogen combination containing ethinyloestradiol (30 µg) and drospirenone (3 mg) is increasingly employed in the
Drospirenone is an analogue of the aldosterone antagonist spironolactone and possesses a similar biochemical and pharmacological profile to that of endogenous progesterone. In a study by Guido et al., treatment with this drug combination was found to be well tolerated, to provide acceptable menstrual cycle control and to produce significant reductions in mean Ferriman–Gallwey score versus baseline.

Finasteride can also be effective in female hirsutism, although it is not indicated for this condition. It inhibits the enzyme 5-alpha-reductase, which converts inactive testosterone to the active form dihydrotestosterone (DHT). Finasteride has been evaluated for treatment of hirsutism in multiple observational and randomized trials. It has been shown to reduce hirsutism scores by 30–60% in many clinical trials, as well as decreasing average hair diameter. In comparative trials, finasteride demonstrated efficacy similar to that of other antiandrogens, with fewer adverse effects.

Furthermore, a prospective, randomised trial of 45 women with hirsutism found significant reductions in hair growth using a treatment regimen of 5 mg finasteride per day, as reflected in a significant decrease in the modified Ferriman–Gallwey score in this treatment group. The main risk with this treatment is that it is contra-indicated in women of childbearing age since it can cause feminisation of the male foetus, as can all anti-androgen drug treatments. Patients prescribed this treatment should be co-administered contraception where appropriate.

Treatment of hirsutism involves a two-pronged approach: reduction of the androgen ‘drive’ and removal of terminal hair. Eliminating androgens once terminal hair growth is present is not sufficient to stop hair growth. It is also necessary to manage clinically associated conditions such as acne and hair loss.

All systemic treatments carry the risk of associated side effects and patients should be advised of these prior to initiation of treatment.

Topical treatment with eflornithine 11.5% cream (discussed later) reduces the rate of hair growth and therefore other methods of hair removal can be undertaken less frequently.

**Mechanical hair removal or depilation**

The choice of removal method depends upon the type of hair, the area being treated and previous treatment history.

There are various options available for mechanical hair removal; e.g. tweezing, depilatories, waxing, shaving, electrical depilation, IPL and laser (discussed later). The former two options, tweezing and depilatory wax should be used with caution as anecdotal evidence suggests that this can potentially exacerbate hirsutism by making the...
hairs grow back more thickly and more coarsely than before. Furthermore, the use of depilating agents can result in worsening of the hair growth if used excessively or indiscriminately3. Another disadvantage that patients should be aware of is that methods such as waxing and tweezing distort the hair, making subsequent treatments (e.g. electrical depilation) more difficult to carry out. The use of plucking and waxing in androgenized skin areas can induce folliculitis and trauma to the hair shaft with the subsequent development of ingrown hairs and further skin damage3. These methods are not addressed here in any detail.

Professional electrical depilation removes or disables the blood supply to the hair itself and is the only method clinically proven to have the potential for achieving permanent hair removal3.

In galvanic depilation a needle is inserted into the hair follicle and a direct current is applied which results in a chemical reaction with the salts in the tissue (electrolysis) leading to the destruction of the hair follicle.

In contrast to galvanic depilation, the diathermic method uses alternating current to induce a heat reaction thus coagulating the hair follicle.

Both methods carry their own advantages and disadvantages. Galvanic depilation is associated with less hair regrowth and is effective for distorted follicles and deep, coarse hairs. However, it is more time consuming, which cuts down the number of hairs that can be treated per session. Diathermic depilation is less time consuming, ideally suited to treating finer, shallow hairs, but is associated with a higher potential for regrowth. The ‘blend’ method combines both approaches depending on the size of the hair to be treated. Professional depilation of this sort is the only method clinically proven to have the potential to achieve permanent hair removal.

Shaving does not affect the hair root and therefore has no effect on hair regrowth, despite popular opinion to the contrary. It is therefore recommended as an ideal means of maintaining hair growth in between other treatments such as electrolysis. However, it should be positioned sensitively as the act of shaving is perceived negatively by patients due to its masculine connotations2. However, there are many razors, both electric and non-electric available designed specifically for women which can help render shaving more of a feminine act. The use of depilatory creams in between treatments is not recommended and it is essential to get a long-term commitment from the client to avoid tweezing or waxing, both of which could adversely affect the success of electrolysis.

Treatment with electrical depilation can take up to 24 months to be effective but varies by hair type, underlying cause, previous treatments, operator skill, client commitment and individual response. Following each successful treatment, the hair will take longer to grow back and will appear less coarse. In the past, concerns were raised as to the potential risk of scarring with this type of hair removal. Scarring can occur as a result of inaccurate probing, excessive or insufficient insertion depth, excessive current, lack of hygiene, adoption of an inadequate healing interval between treatments (should be 7–14 days) or lack of appropriate aftercare. In order to minimise the risk of infection or scarring, it is essential that patients are advised to consult qualified skilled treatment operators with extensive experience in this area.

Laser treatment

The use of lasers to remove unwanted hair is the fastest growing modern procedure and provides a safe and rapid hair removal method for long-term use. Recently, a number of lasers have been developed specifically to target hair follicles offering the potential for rapid treatment of large areas and long-lasting hair removal22.

Laser light passes through the surface of the skin, is absorbed by melanin (the only endogenous chromophore pigment, located in the follicle) and is converted into heat energy, destroying the hair tissue. The target region is the stem cell population which consists of modified outer root sheath cells. In this region the cells proliferate very rapidly in the growing phase (anagen) of the hair cycle. Pigmented cells are concentrated in this cell population. This means that laser hair removal is most effective when hair is in the anagen phase.

Although there are various laser systems available for the reduction of unwanted hair, no single system has been shown to provide superior in terms of providing safe and effective hair removal in every skin type23. If the laser pulse is too long, this can result in heat damage to surrounding tissue, which can result in scarring. Clinical experience suggests that darker skin is best treated with longer wavelength lasers.

Hair counts are successively reduced after each laser treatment which can make shaving of the affected area unnecessary in some cases24. While long-term hair reduction can be obtained in most patients after a series of laser treatments, partial hair regrowth typically occurs within 6 months, making additional treatments necessary24. Complete hair loss is rarely achieved3.

The ideal patient for treatment with laser hair removal is fair skinned with dark hair. Dark skin carries the risk of epidermal damage such as scarring or dyspigmentation. It is important that patients are accurately informed of the process and the potential risks of laser treatment such as dyspigmentation, itching and pain.
Advances in laser technology over the past decade have spawned the development of numerous red and infrared lasers and light sources for use in the treatment of unwanted facial and body hair. Such treatments have yielded promising results in the clinical arena although to date there has been a paucity of long-term comparative studies. Research has shown that regardless of the laser system used, the optimal clinical response is achieved 1 month after the second laser treatment, with prolonged clinical hair reduction seen 6 months after the third and final treatment. This is irrespective of the laser system used.

In a retrospective study of 242 patients carried out by Kopera et al., the efficacy of an 800 nm diode laser over a period of 48 months was evaluated. This study found that sufficient reduction of pigmented hair was achieved after an average of 1.97 treatments for a mean time period of 8.1 months. Patients were also able to lengthen the time in between plucking from four to 15 days after laser therapy for hair removal. This study supports the use of 800 nm diode laser for the reduction of pigmented hair. Reductions in hair count of up to 46% versus baseline after 9 months of treatment have been shown in research using long-pulse lasers.

A randomized controlled trial of 88 women with hirsutism due to PCOS found that laser treatment reduced self-reported severity of facial hair, mean depression scores and mean anxiety ratings by a significantly greater amount in the treatment group versus controls over the 6-month study period.

Topical treatment

Eflornithine 11.5% cream (Vaniqa, Shire Pharmaceuticals, UK) is a topical treatment which slows hair growth and thickness. It works by specifically and irreversibly inhibiting the enzyme ornithine decarboxylase which catalyses the conversion of ornithine to putrescine, one of the polyamines critical to the regulation of cell growth and differentiation (Figure 1).

Eflornithine inhibits ornithine decarboxylase, an enzyme key to the synthesis of polyamines. When polyamines, which are involved in the proliferation of matrix cells, are inhibited, the rate of hair growth is reduced.

Inhibition of the ornithine decarboxylase enzyme in the hair follicle slows the rate of hair growth and makes the hairs less visible and less coarse. Eflornithine cream has been extensively studied in the clinical arena in over 1800 patients in both phase II and phase III trials.

A thin layer of eflornithine cream is applied to clean, dry skin in the affected area twice daily. Cosmetics such as sunscreen can be used on eflornithine-treated areas, from 5 minutes after application. Systemic medications for hirsutism (e.g. metformin, cyproterone acetate) and mechanical hair removal methods (e.g. shaving, plucking, laser and electrical depilation) can be used in conjunction with eflornithine cream.

In a randomised, double-blind, vehicle-controlled trial, eflornithine significantly reduced facial hair growth compared with placebo vehicle cream within 8 weeks of treatment with at least 70% of women responding favourably to treatment. Significantly more patients were classified as clinical successes (patients showing a considerable reduction in the visibility of terminal hair, or no or almost no visible terminal hair, in the eflornithine group at 8 weeks compared with the placebo group [p = 0.05]). Not only was hair density reduced following treatment but there was also a marked benefit in psychological factors such as reduced social discomfort leading to an improved quality of life.

Preliminary results from long-term studies are equally promising. After 6-months of treatment with eflornithine, at least 47% of women were classed as treatment successes (marked improvement or better) and 90% of women overall showed some level of improvement. At 12 months, 80% of women showed some level of sustained improvement and 24% were classed as treatment successes, demonstrating the long-term efficacy of eflornithine in the treatment of unwanted facial hair.

Continued treatment with eflornithine cream is needed to maintain efficacy as the benefits of treatment diminish to some degree 8 weeks after cessation of treatment.
therapy. This is because, unlike treatments for male-pattern baldness, which work on the hair cycle as a whole, eflorenithine works by inhibiting each individual hair in the anagen or growth phase.

Data from preliminary studies have shown that the combination of laser therapy and eflorenithine can give superior improvements in hair removal compared with the use of laser therapy alone. Results of a randomized, vehicle-controlled, double-blind trial found that concomitant use of the two treatments yielded a synergistic effect with respect to onset and degree of hair removal versus laser therapy alone.

Data from dermal safety studies found that eflorenithine cream did not induce any contact or photocontact sensitisation reactions. Combined results from two, double-blind, randomised, multi-centre, comparative studies (n = 596) found that adverse events were generally mild, transient and resolved without the need for dose reduction. The percentage of subjects reporting adverse events was comparable for the eflorenithine and vehicle groups. The most common treatment-related adverse events were skin related with only burning, stinging and tingling occurring significantly more frequently in the eflorenithine treated subjects versus the vehicle-control group.

Overall, eflorenithine cream has been shown to significantly improve hair growth in approximately 60% of women with excessive facial hair, with such improvements being noticeable as early as 8 weeks into treatment. If no treatment benefit with eflorenithine is seen after four or more months of therapy, it should be stopped as it is not likely to be effective.

Conclusions

There are various strategies which can be employed for the effective management of female hirsutism. The combination of mechanical hair removal techniques, such as laser therapy, and topical treatments offers an effective, long-term solution. Eflorenithine has been shown in preliminary trials to reduce the rate of hair growth and can be used successfully in combination with all hair removal methods. Further research is needed to further support these findings. These treatment strategies may be carried out in conjunction with hormonal therapy where indicated, depending upon the aetiology of the case concerned.

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