Medical Treatment of Hirsutism in Women

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Abstract: Hirsutism is the presence of excess hair growth in women in the typical male hair growth areas, thereby reflecting a deviation from the normal female hair pattern. It affects from 5% to 10% of women, depending on age, menopausal status and ethnic background. The presence of hirsutism is very distressing for women, and subsequently may have a negative impact on their psychosocial life. In the treatment of hirsutism several options are now available, including pharmacologic regimens and cosmetic measures. Both the hormonal profile of the patient and her expectations and preferences should guide the therapeutic approach. The aims of the medical therapy are suppression of excessive androgen production, inhibition of peripheral action of androgens, and treatment of patients at risk for metabolic disorders or reproductive cancers. For other diseases related to endocrine abnormalities, such as thyroid disorders or Cushing's syndrome, specific treatment is mandatory. After an ineffective local approach by direct hair removal, a pharmacological treatment should be suggested, using estrogen and progestin combinations, antiandrogens (i.e. cyproterone acetate, spironolactone) or both as a first line. Finasteride, gonadotropin-releasing hormone agonists, and glucocorticoids should be used in selected cases. Adequate contraception is also recommended if antiandrogens are used. Unfortunately, since systemic therapy reduces hair growth in less than 50% of cases, hirsute women frequently require cosmetic measures. The use of a logical combination of different options has been shown to achieve a satisfactory result in most cases. This review provides information and suggestions about the current options of treating hirsutism.

Keywords: Hirsutism, hypertricosis, hyperandrogenism, antiandrogens, oral contraceptives, spironolactone, cyproterone acetate.

INTRODUCTION

Hirsutism is the presence of excess hair growth in women in the typical male hair growth areas, thereby reflecting a deviation from the normal female hair pattern [1]. Hirsutism affects from 5% to 10% of women, depending on age, menopausal status and ethnic background, but for a correct clinical evaluation, the type of hair (see below) growing should be described [2]. In any case, the presence of hirsutism is very distressing for women, and subsequently may have a negative impact on their psychosocial life [3, 4].

Although 70-80% of patients with androgen excess may have hirsutism, only a minority of hirsute women have detectable androgen excess [5]. *Idiopathic hirsutism* is the most common nonpathologic cause of hirsutism, accounting for over 50% of patients [6]. It is defined as a condition in which hirsute women have normal ovarian function (regular menses and ovulatory cycles), normal circulating androgen, and an absence of virilization. Unfortunately, the cause of excess of hair growth in patients with idiopathic hirsutism is unknown, but an increased 5α-reductase activity (5α-RA) has been found in most of these women [6, 7].

REGULATION OF HAIR GROWTH

The body is covered by millions of hair follicles, the number of which is determined at birth [8]. The skin follicular units vary not by gender but by ethnic origin, and hair distribution is correlated to the distribution of hair follicles. Their number never increases during life, but gradually decreases with age, especially in men [8, 9].

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There are three different types of hair [10]: (i) lanugo (thin, short and soft hair typical of babies; (ii) vellus (fine, soft and non-pigmented); (iii) terminal (coarse, pigmented and longer than vellus hair). At puberty, under the effects of androgens, a transformation of vellus hair into terminal hair occurs, and the adult distribution of hairs becomes progressively evident.

Hair growth is a result of three phases, the length of which varies widely. The first is the active growing phase (anagen), that lasts from two to six weeks depending on skin region. Anagen is followed by the stopping of growth (catagen), which is a shorter (2-3 weeks) phase. When the keratinization of hair is completed, it enters a resting phase (telogen), and a new matrix is gradually formed [9, 11]. The ratio of hair in the growing phase to those in resting phase (anagen-telogen ratio) may be used to estimate the hair growth status in a specific area [9]. Hair of the forearm has a short anagen phase and a long telogen phase, while hair on the head has a very long (2-3 years) anagen phase and a short telogen phase, resulting in constantly growing hair [6]. The main endogenous factors affecting the hair growth are reported in Table **1**.

PATHOPHYSIOLOGY AND CLINICAL FEATURES

Hirsutism results from a pathological relationship between sensitivity of androgen receptors on skin to circulating androgens and the levels of circulating androgens [12].

Hair follicles have receptors only for dehydrotestosterone (DHT), and the enzyme 5α-reductase converts testosterone and other androgens to DHT [13, 14]. It is well known that 5α-RA and DHT are the main determinant of male-type hair distribution and growth in women, and androgen-dependent hair growth may me reduced by (i) decreasing androgen production, (ii) reducing androgen conversion to DHT, and (iii) blocking androgen receptors [8, 14].

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Table 1. Main Endogenous Factors Affecting Hair Growth [11]

Decreasing	Increasing
Epidermal growth factor (EGF)	Basic fibroblast growth factor (bFGF)
Fibroblast growth factor type 5 (FGF-5)	Insulin-like growth factor I (IGF-I)
Interleukin 1-alpha (IL-1-α)	Platelet-derived growth factor (PDGF)
Transforming growth factor beta (TGF-β)	

All circulating steroids are bound to plasmatic proteins, such as albumin and sex hormone-binding globulin (SHBG), and only 1% of testosterone and 5% of androstenedione are free and biologically active [13]. Several conditions may decrease or increase the serum SHBG levels, modifying the free androgens' serum levels (Table **2**).

Table 2. Main Conditions in which Decreasing or Increasing SHBG Serum Levels may be Observed [13]

Decreasing	Increasing
Hypothyroidism, obesity, corticosteroid therapy	Pregnancy, hyperthyroidism, cirrhosis, estrogen therapy

Both hirsutism and virilism are related with excessive ovarian or adrenal secretion of androgens, or excessive peripheral conversion of androgens. However, in adults, virilism and severe androgen excess are usually observed only in the presence of androgen-secreting ovarian and adrenal tumors [15]. Hair change are also observed in some endocrine diseases (Table **3**). Moreover, there are several drugs that may produce adverse effects on hair growth (Table **4**).

Table 3. Type of Hair Changes in Patients with Endocrine Diseases [15]

Hirsutism	Increased body hair
Androgen excess, acromegaly, Cushing's syndrome, polycystic ovary syndrome	Cushing's syndrome, hypopituitarism, hypothyroidism, thyrotoxicosis

Table 4. Main Drugs Producing Hair Growth or Loss [11]

Hair growth	Hair loss
Anabolic steroids, testosterone, ACTH, minoxidil, cyclosporine, diazoxide	Cytotoxic drugs, amphetamines, β-blockers, ibuprofen, interferon, lithium, salt of gold

The *evaluation of hirsutism* is usually clinical, and three types of evaluations are available [16].

- Objective: Hair shaft diameter, hair shaft length, hair shaft weight
- Semi-objective: Ferriman-Gallwey score, changes in hair removal frequency, changes in hair distribution score
- Subjective: Patient's personal observations, quality-of-life.

The Ferriman-Gallwey score rates the patient on a scale from zero (absence of terminal hairs) to 4 (extensive hairs), according to the density and distribution of terminal hairs in different areas of the body: chin, upper lip, chest, upper back, lower back, upper abdomen, lower abdomen, arms, thighs, and lower legs [17]. Hirsute women should be those with a score of 6 to 8 or greater.

Hirsutism is usually considered the result of an atypical relationship between sensitivity of androgens receptors on skin to circulating androgens, and their levels in blood [18]. In patients with mild or moderate hirsutism and regular menses, a hormonal evaluation is considered unnecessary, since they rarely have an underlying disease and overt hyperandrogenism [1]. Testing for elevated androgens blood levels should be suggested for women with moderate or severe hirsutism of sudden onset or rapid progression, virilization, menstrual irregularity, or obesity [19].

TREATMENT OF HIRSUTISM

In the treatment of hirsutism several options have been suggested and are now available, including pharmacologic regimens and cosmetic measures [18]. Unfortunately, the overall quality of the studies concerning effectiveness of treatment is limited, because they are based on small series, no clear quality-of-life outcomes, and short follow-up [20]. However, some authoritative reviews have been published recently, and a guideline from The Endocrine Society is also available [19].

The aims of therapy are: (i) suppression of excessive androgen production, (ii) inhibition of peripheral action of androgens, and (iii) treatment of patients at risk for metabolic disorders or reproductive cancers. For other diseases related to endocrine abnormalities, such as thyroid disorders, or Cushing's syndrome, specific treatment is mandatory.

Being often caused by an underlying endocrine disorder, treatment of hirsutism should be focused on hormonal alteration. Also in idiopathic hirsutism, the prevention and early treatment of patients with a history of excessive hair growth should be achieved [9].

Treatment can be systemic or non-systemic, pharmacological or non-pharmacological. To be effective, it should follow a complete diagnostic work-up and should be tailored to the clinical profile and preference of the patients.

Pharmacological therapies can be divided into two main categories: those suppressing ovarian and adrenal androgen secretion, and those inhibiting androgen action on hair follicles. Different medical therapies, alone and in combination, have been used to treat idiopathic hirsutism [3, 18]. They include:

- Inhibitors of androgen production (estrogen and progestin combinations, gonadotrpin-releasing hormone agonists)
- Peripheral androgen blockers (cyproterone acetate, spironolactone and flutamide), enzyme inhibitors (finasteride)
- Insulin-sensitizing agents (metformin, rosiglitazone).

Since the response to medical treatment is slow, combination with cosmetic measures is usually required [14]. Systemic therapies inhibit the anagen phase, usually stimulated by androgens. Thus, the number of follicles passing through the anagen phase influences the clinical and visible effect.

Cosmetic measures are usually the first step of treatment, and include mechanical hair removing (i.e. shaving, plucking), depilatory creams, electroepilation and laser- or photoepilation [21]. The results of physical and chemical epilation are only short-term and may lead to several adverse effects, such as pain, skin redness, swelling, infections, alterations of skin pigmentation [22-23]. Epilation techniques are usually complementary to pharmacological treatment, and are used to obtain a rapid effect and improve the patient's quality of life as quickly as possible. The site to be treated, the colour of the hair, and also the financial budget, all affect the patient's choice [18].

Chemical epilation includes different techniques such as sugaring, depilatories, and bleaching with hydrogen peroxide preparations. Most depilatory creams are based on thioglicolates and are less irritating, but inflammation and lesions of the epidermis are the major disadvantages of these methods.

Electrolysis and electroepilation are characterized by the application of electricity directly to the hair follicles, through a probe. A hair-thin metal probe is slid into a hair follicle. Electricity is delivered to the follicle through the probe, which causes localized damage to the areas that generate hairs. The combination of galvanic electrolysis and high frequency alternating current (thermolysis), called "blend method", is considered the most effective technique, with reduced side-effects. It is a well known technique, and the first clinical applications were reported in 1875 [24]. Electrolysis satisfactorily removes hair, but hirsute women can require concomitant management of their hormonal problems. The technique may be painful, tedious and expensive, due to the fact that only 100 hair follicles can be treated per session, but an effective control of facial hirsutism may be obtained in up to 90% of patients [25, 26].

The principle for hair removal with laser devices and intense pulsed light (IPL) is based on photodermolysis, which causes a thermal damage of the pigmented part of the follicle, without destroying adjacent tissues [27]. Light at a specified wave-length is delivered from a handpiece into the skin, where it targets dark material (usually the pigment in hair). Skin type and melanin content of hair (blond, red and white hairs are not suited for laser epilation), determine the final result [28]. The modern lasers operate in the red or near-red wave-length. The treatment of hirsutism with laser and IPL is an effective option that improves the quality of life of patients. Thus, long-lasting or permanent hair-removal is mainly based on the number of sessions [29]. Using an alexandrite laser, a 40% reduction of hair growth was found, while less effective results were reported with Nd:YAG laser, ruby laser and IPL [30, 31]. The terms "permanent hair reduction" often reported by some manufacturers is confusing and unrealistic for people, since no published clinical data can substantiate this statement [30]. High costs and several adverse effects were reported and should also be considered [23, 32, 33].

Eflornithine is a topical agent that inhibits the enzyme ornithine decarboxylase, which reduces matrix cell proliferation and blocks hair growth. Balfour *et al.,* in a double-blinded and placebo-controlled trial, reported a maximum effect between 8 and 24 weeks, with significant improvement in treated patients (32% *vs.* 8% treated with placebo) [34]. Another study showed a 26% facial hair reduction after 24 weeks of treatment [35]. Eflornithine cream can be safely used alone and in combination with laser and IPL treatments, with insignificant systemic absorption [36].

The mainstay of *pharmacological treatment* is suppression of androgen secretion and/or inhibition of peripheral action of androgen receptors. This goal can be achieved with different drugs, used as mono-therapy or combined in different regimens (Table **5**). A recent review found that the pharmacological suppression of hirsutism at 6 months may range from 19% to 41%, according to different drugs [37].

Table 5. Main Treatment Options of Hirsutism [18]

Physical & local methods:
• Laser • Intense pulsed light • Electrolysis & electroepilation • Physical & chemical epilation
Oral contraceptives
Antiandrogens & enzyme inhibitors :
• Cyproterone acetate • Dienogest • Spirinolactone • Drospirenone • Flutamide • Finasteride
Gonadotropin-releasing hormone agonists
Insulin sensitising agents:
• Metformin • Thiazolidinediones
Glucocoriticoids

Estrogen and Progestin Combinations

Oral contraceptives (OC) inhibit ovarian androgen production by suppressing circulating LH and FSH. They contain an effective synthetic estrogen (ethinylestradiol [EE]) and a progestin. Being LH the primary driver of ovarian androgen secretion, OC are useful especially in patients with polycystic ovary syndrome (PCOS), and LH-dependent androgen secretion [14]. The effect of OC depends on the content of EE (20-35 μg), which stimulates the production of SHBG, and the nature of the progestin, which increases the

metabolic clearance of testosterone. Progestins with antiandrogenic properties can be favorably prescribed in hirsute women, whereas those containing levonorgestrel and norethisterone may have an androgenic effect [38]. Progestins alone increase testosterone clearance and suppress LH, but do not increase SHBG, and are usually less effective. In patients with idiopathic hirsutism, OC normalize circulating androgens, but usefulness of OC alone in such patients is not proven [9]. New progestins (i.e. desogestrel, gestodene) have a neutral androgenic effect, and are considered the drugs of choice, usually associated with an antiandrogen [39-40]. Efficacy of the addition of antiandrogens to OC is not supported by qualified trials [41]. A recent systematic review suggested a benefit of such combination, but addition of high (100 mg) doses of cyproterone acetate (CPA) to OC (containing 2 mg CPA) did not improve results [42]. For premenopausal women, OC are suggested by The Endocrine Society in their Clinical Practice Guidelines (Table **6**) [19]. Adequate contraception is also recommended if antiandrogens are used, because of their teratogenic potential.

Antiandrogens and Enzyme Inhibitors

Antiandrogens block the cellular action of androgens. They competitively inhibit androgen binding to the receptors, or inhibit the enzyme 5α-RA [12].

Cyproterone acetate is a chlormadinone acetate derivative, with progestational and antiandrogenic activity. The effect is due to the suppression of LH secretion, the inhibition of androgens binding to the receptors (competitive action with DHT), and in a lesser degree to the inhibition of 5α-RA [14]. CPA, alone or combined with estrogens, is used worldwide to treat hirsutism, but is not available in the USA. Its long half-life (about 30 hours) allows a reverse sequential way, combined with EE (given on days 5 to 25, to normalize the menstrual cycle). CPA is administered from day 5 to 25, at the dose of 50-100 mg daily, and then continued at the lower effective dose (usually 5 mg/day) for maintenance [19]. Van der Spuy *et al.* reported that CPA at the dose of 2 mg/day was more effective than placebo, but not than any other antiandrogen (ketoconazole, spironolactone, flutamide, finasteride and gonadotropin-releasing hormone agonists) [43]. Venturoli *et al.* reported that CPA (50-100 mg) combined with EE (30-35 μg) was more rapid and effective than flutamide, ketoconazole and finasteride [44]. Similarly, we have previously shown that F-G score decreased 39% in patients treated with an oral contraceptive plus CPA (12.5 mg/day for the first 10 days of the cycle) [2]. A satisfactory clinical outcome was found in 90% of patients treated with CPA (2 mg/day) and EE, but relapse was reported in 80% of women 6 months after withdrawal [45]. However, most studies are based on the use of the F-G score to assess clinical results, which is less accurate than linear hair growth and hair shaft diameter, and may affect results [43]. CPA is usually well tolerated, but an increased risk of venous thromboembolism in women treated with OC and CPA has been reported, in comparison with those treated with levonorgestrel [46]. Other rare side effects include loss of libido, and the risk of feminizing a male fetus [9]. Unfortunately, the real incidence of side effects is controversial, because of limited studies available [43].

Dienogest is a hybrid progestin, with a high selectivity for progesterone receptor and a half-life of 9 hours after multiple doses [47]. It shows antiandrogenic effect, but only light antigonadotrophic activity. Side effects are similar to the other progestins, but no androgenic adverse effects are

Table 6. Treatment of Hirsutism in Premenopausal Women According to The Endocrine Society Guidelines. Grade 1 and 2 Means Strong and Weak Recommendations, Respectively. The Number of + is the Quality of Evidence. Modified from Martin *et al.* [19] and Swiglo *et al.* [42]

Indications	Grade
Suggestion of laser/photoepilation for women, who choose hair removal approach	2 ++
Suggestion of adding eflornithine cream to photoepilation for women who want a more rapid response to therapy	2 ++
Suggestion of pharmacological treatment or direct hair removal for women with patient-important hirsutism, after ineffective cosmetic approach	2 ++
Suggestion of OC or antiandrogens in women, who cannot or choose not to conceive	2 ++
Suggestion of OC for treatment of patient-important hirsutism	2 ++
Suggestion of adding an antiandrogen after 6 or more months of non-effective therapy with OC	2 ++
Recommendation of adequate contraception if antiandrogens are used	1 +
Suggestion of treatments of at least 6 months for all drugs, before making any changes in dose, type or addition	2 ++
Suggestion against the use of topical antiandrogens	2 ++
Suggestion against the use of flutamide	2 ++
Suggestion against the use of insulin-lowering drugs	2 ++
Suggestion against use of GnRH agonists, except in women affected by severe hyperandrogenism, who have a suboptimal response to OC and antiandrogens	2 ++
Suggestion of glucocorticoids for hirsute women due to non-classic congenital adrenal hyperplasia, who have a suboptimal response or intolerance to OC and / or antiandrogens, or are seeking ovulation induction	2 ++

OC = oral contraceptives, GnRH = gonadotropin-releasing hormone.

reported and clinically effects on metabolic, lipid and haemostatic parameters are insignificant [48]. Unfortunately, no specific and significative clinical trials are yet available on this drug.

Spironolactone is an aldosterone antagonist with antiandrogenic properties, which acts through several mechanisms: competition with DHT for androgen receptors in the skin, increase of SHBG levels, inhibition of 5α-RA and other enzymes, increase of testosterone clearance and liver hydroxylase activity, and progestational activity [49]. Its half-life after multiple doses is 13-24 hours, and the daily dose ranges between 100 and 300 mg. A dose of 100 mg/day of SPA reduced significantly F-G score, when compared to placebo [16]. Erenus *et al.* reported better results when SPA-OC was compared with finasteride, while no difference was found between SPA-OC and CPA-EE regimens [50, 51]. SPA is effective also as a single drug, when compared with CPA plus EE at long-term follow-up [52]. We compared SPA 100 mg/day with CPA 12.5 mg/day (for the first 10 days of the cycle) and finasteride 5 mg/day. The combination of SPA and a monophasic OC was found to be superior in reducing the F-G score in the long-term, while no significant differences were noted in the short-term [2]. In our study, reduction of serum androgen levels was not significant, but these levels are thought to be not necessarily related with the clinical effect [43]. A recent review confirmed that SPA is an effective therapy [16]. We would suggest that this is particularly true for hirsute women in whom OC alone is ineffective. SPA is usually well tolerated, but an association of SPA and OC is suggested, because of a dose-dependent effect of menstrual irregularity and for the risk of fetal malformations. Side effects, related to the anti-aldosterone activity, such as hypotension, polyuria and headache are occasionally reported. Blood pressure and renal function should be monitored in the first months of treatment, even if no significant changes were observed at long-term follow-up with no more than 100 mg daily, but renal insufficiency represents a contraindication [9].

Drospirenone (DRSP) is a progestin with a weak antiandrogen activity. OC containing DRSP and CPA are used in treatment of facial hirsutism, and the DRSP/EE regimen is at least as effective as the CPA/EE one in treating hirsutism [53]. Gregoriou *et al.* found that a combination of DRSP (3 mg) and EE (30 μg) was able to reduce F-G score to 77.4% and 51.8% after 3 and 12 months of treatment, respectively [54].

Flutamide is a pure, non-steroid androgen receptor blocker, with a dose-response action, that has been used as adjuvant treatment for prostate cancer [55]. Its half-life is about 6 hours, and the dosage in hirsute women varies from 250 to 500 mg daily. Flutamide was found to be the fastest acting drug in decreasing hair diameter, however no significant difference between flutamide and SPA plus CPA/EE was found at long-term [44, 56]. Similarly, when compared to a regimen with flutamide plus OC, no differences in clinical results were reported [41]. More recently, Unluhizarci *et al.* compared three different regimens with flutamide, finasteride, and finasteride plus flutamide. The improvement in F-G score was 24%, 35% and 33%, respectively, showing that flutamide is more effective than finasteride, and that the addition of flutamide to finasteride is not useful [57]. Several side effects have been reported (appearance of greenish urine, dryness of the skin, liver enzyme alteration), including severe hepatotoxicity, and thus this drug should not be considered a first-line therapy for hirsute women [19].

Finasteride (FNA) is a potent, competitive inhibitor of the type 2 isoenzyme 5α-RA, reducing DHT without altering ovarian and adrenal androgen secretion [18]. It has no other known hormonal activity, and so can be safely used in hirsute women [58]. Its half-life is 6-8 hours and the dose varies from 1 mg to 5 mg/day. Recent studies report different improvements of hirsutism score, ranging from 30% to 60% [55, 59, 60]. In a comparative trial FNA was found to be as effective as other antiandrogens, but with less side effects [28]. Venturoli *et al.* found that FNA was effective in reducing F-G score (44%) and hair diameter (16%) after 12 months of treatment [44].

Other Drugs

Gonadotropin-releasing hormone (GnRH) agonists suppress the hypothalamic-pituitary-ovarian axis, inhibiting LH and FHS, thereby decreasing the production of ovarian androgens [28]. Long-acting GnRH agonists can be administered monthly, such as triptorelin 3.75 mg/month, but 2 or 3 months of therapy are needed prior to a clinical effect. Several studies have found significant reductions in F-G score using GnRH analogs, but have weak evidence [18]. An uncontrolled trial found that leuprolide acetate was more effective (36% *vs.* 14%) than finasteride alone in reducing F-G score [61]. However, when compared with OC, flutamide or CPA, they do not show any advantage, although GnRH agonists with add-back treatment appear to result in a longer remission of hirsutism in comparison with CPA [62-65]. GnRH agonists are expensive, need an estrogen-progestin replacement therapy, and would be better used in patients with severe hyperandrogenism [19].

Insulin-sensitizing agents include metformin and thiazolidinediones (TZDs), and are widely used in patients with noninsulin-dependent diabetes mellitus with the aim of reducing glycemia, and increasing insulin sensitivity [1, 3]. Insulin also acts as a co-gonadotropin, and is a secondary driver of ovarian steroidogenesis [66]. Metformin reduces hepatic glucose production and improves insulin sensitivity, while TZDs improve insulin action in the liver, skeletal muscle and adipose tissue, both increasing SHBG and reducing circulating free androgens [67]. The half-life of metformin and TZDs ranges between 3 and 7 hours. A recent review confirmed that metformin is effective for inducing ovulation in patients with PCOS, and improves androgen levels and hirsutism [68]. Yilmaz *et al.* compared metformin and rosiglitazone in patients with PCOS, finding that rosiglitazone had a better long-term result [69]. However, when compared with antiandrogens (SPA, flutamide) the results were not positive [19]. When metformin is compared with OC, no significant difference in F-G score was found [70]. Cosma *et al.* in a recent metaanalysis concluded that insulin-sensitizing agents did not show any advantage when compared with OC and antiandrogens, and may have a role only in correcting hormonal disturbances in women with PCOS [3]. Obese patients, who should avoid OC because of the risk

Table 7. Treatment Options of Hirsutism According to the Main Clinical Findings of Women. Modified from Koulouri & Conway [20]

Non-obese premenopausal women
In absence of risk factors for thrombosis, OC containing CPA or drosperinone is appropriate Eflornithine cream can be added for 12 weeks if rapid hair growth suppression is requested After 6 months of ineffective treatment, an antiandrogen (i.e. CPA, SPA) can be added Occasional non-respondent cases may need the addition of FNA
Obese women with PCOS
Promotion of weight loss is needed A combination of SPA and metformin can be used as first line treatment
Congenital adrenal hyperplasia
Glucocorticoids may optimize adrenal secretion Antiandrogens are usually non-effective Treatment with laser is a valuable approach
Perimenopausal women
Lack of evidence in this condition affects therapeutic options Estrogens, usually together with an antiandrogen (i.e. drosperinone) or SPA, can be used in mild hirsutism. GnRH agonists are recommended for severe hirsutism, but oophorectomy should be considered

OC = oral contraceptives, CPA = cyproterone acetate, SPA = spironolactone, FNA = finasteride, PCOS = polycystic ovary syndrome, GnRH = gonadotropin-releasing hormone.

of thrombosis, may benefit from insulin suppression, but long-term treatment with these agents is not risk-free, and an increased risk of cardiovascular events has been reported [20, 71].

Glucocorticoids suppress ACTH-dependent adrenal androgen synthesis, which is typically present in congenital adrenal hyperplasia (CAH), due to 21-hydroxylase deficiency [28]. Relative adrenal hyperandrogenism is present in hirsute women with PCOS, and in those with classical and non classical CAH [1]. Adrenal hyperandrogenism can benefit from glucocorticoid therapy. Low doses do not inhibit cortisol secretion, but a suboptimal testosterone suppression is obtained, while higher doses are associated with side effects related to hypercortisolism [72]. Spritzer *et al.* treated hirsute women with CPA or hydrocortisone. F-G score at 1 year improved 54% in the CPA-group, and 26% in the other group. Differently, androgen levels were normalized only in the hydrocortisone-group, emphasizing the role of peripheral androgen receptors in the clinical picture of hirsutism [73].

Table 8. Pharmacological Options Available to Treat Hirsutism, and their Side Effects. EE=Ethynil Estradiol, PGs=Progestins

Class of drugs	Main Drugs	Side effects
Oral contraceptives (inhibition of ovarian androgen production: EE increases SHBG, PGs increase clearance of testosterone)	Ethynil estradiol plus Progestins with neutral antiandrogen effect (i.e. Desogestrel, Gestodene) PG with weak antiandrogen effect (Drospirenone) PG with antiandrogen activity (CPA, CMA, Dienogest)	Breast tenderness, headache, gastrointestinal symptoms Hyperkaliemia, alteration of liver and renal function Increased risk of venous thromboembolism* and steroidal side effects (CPA), liver function abnormalities, menstrual irregularities, risk of feminizing of male fetus
Antiandrogens (block cellular action of androgens: receptor competition and weak inhibition of 5α-RA) *(no FDA labeling for treatment of hirsutism)*	Cyproterone acetate Dienogest (PG with anti-androgen activity) Spironolactone	Increased risk of venous thromboembolism and steroidal side effects, liver disfunction, risk of feminizing of male fetus No significant effects on metabolic, lipid and haemostatic parameters Hyperkaliemia and renal disfunction, gastritis, blood lipid alterations (decrease of HDL and increase of LDL), hypotension, menstrual irregularities, gynecomastia, risk (possible) of feminizing of male fetus, headache
	Finasteride	Risk of feminization of male fetus, liver disfunction (rare)
	Flutamide	Liver toxicity, nausea, diarrhea, skin alterations (dryness)
Gn-RH agonists (inhibition of ovarian androgens production) *(no FDA labeling)*	Leuprolide Triptorelin	Hypoestrogenic effects (atrophic vaginitis, hot flushes, decreased bone mineral density)
Glucocorticoids (suppress ACTH-dependent adrenal androgen synthesis) *(no FDA labeling)*	Dexamethasone Hydrocortisone	Hypercortisolism (hypokaliemia, weight gain, decreased BMD)
Insulin-sensitizing agents (Increasing of SHBG, co-gonadotropic action of insulin) *(no FDA labeling)*	Metformin & Thiazolidinediones	Gastrointestinal distress, increased risk of cardiovascular events, lactic acidosis (rare with high mortality), interactions with many other drugs, liver disfunction

*risk of thromboembolism related to use of different PGs (from + to +++): Levonorgestrel +, Norethisterone +, Gestodene ++, Desogestrel ++, Drospirenone +++, Cyproterone acetate +++ [78].

FUTURE PERSPECTIVES

It has been shown that medical treatment of hirsutism is effective in 19-41% of cases at 6 months [37]. Thus, a careful evaluation of the patient is always requested, to identify the best treatment for the underlying disease and for the psycho-sociological habitus of the patient. Recently, attractive developments have been made in the field of 5α-reductase inhibitors. The inhibition of this pivotal enzyme has become the pharmacological strategy for the synthesis of new antiandrogenic compounds [74]. Different compounds (pregnane derivatives) has been synthesized, they are cheap, and many of them (i.e. compound 5) show high activity and less side effects. Thus, these steroidal derivatives may represent an effective alternative in androgen-dependent diseases [75].

Particularly, 17β-hydroxysteroid dehydrogenases (17β-HSDs) are involved in oxi-reduction of estrogens and androgens, fatty acids and bile acids *in vivo*. Fifteen isoforms have been recognized, and their activity regulates the amount of active steroid available to bind a particular receptor [76]. Thus, inhibition of 17β-HSDs may be very effective in the treatment of several estrogen- and androgen-sensitive disease. However, none of these inhibitors has been tested in clinical trials, but they were very effective in *in vivo* disease models [77].

CONCLUSIONS

Hirsutism is a common problem, which causes discomfort and psychosocial problems in affected women. Various treatments are available, including pharmacologic regimens and direct methods to reduce unwanted hair growth. Thus, both the profile of the patient and her expectations and preferences should guide the therapeutical approach. A long follow-up is required, to monitor results and prevent unsatisfactory outcomes, since systemic treatments reduce hair growth around 25-30% at most [20]. The use of a logical combination of different options has been shown to achieve a satisfactory result in most cases. Table **7** reports the treatment options of hirsute women, according to the main clinical groups, while Table **8** resumes all pharmacological options available to treat hirsutism, and their side effects.

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