SciForschen
Open HUB for Scientific Research

ISSN 2380-548X

International Journal of Endocrinology and Metabolic Disorders

Review Article | Volume: 3.3 | Open Access

Hirsutism, What to do?

Maria Palmetun Ekback*

Department of Pharmacology and Therapeutic, Orebro University Hospital, Region Orebro County, Sweden

***Corresponding author:** Maria Palmetun Ekback, Head of the Pharmacology and Therapeutic Department, Orebro University Hospital, Region Orebro County, Sweden, **E-mail:** maria.palmetun-ekback@regionorebrolan.se

Received date: 14 Jul 2017; **Accepted date:** 10 Oct 2017; **Published date:** 17 Oct 2017.

Citation: Ekback MP (2017) Hirsutism, What to do? Int J Endocrinol Metab Disord 3(3): doi http://dx.doi.org/10.16966/2380-548X.140

Abstract

Hirsutism, excessive hair growth in women in a male pattern distribution, is the most common endocrine disorder in women and approximately 5 to 15% of the general population of women is reported to be hirsute. It causes profound stress in women. Polycystic ovary syndrome is the most common cause. However a woman could have normal menses, normal androgen levels but be hirsute (idiopathic hirsutism). Ferriman- Gallwey scale (F-G) is used for assessment of hairiness. The maximum score is 36 and a score over 8 is considered as a hirsuid state. As hirsutism is a symptom and not a disease it is important to find the underlying cause and exclude uncommon but serious causes. The aim of the medical treatment is to correct the hormonal imbalance and thereby stop further progress. Oral contraceptives (OCP) are recommended as first line treatment. Spironolactone is the first choice if there is indication for antiandrogen therapy. Antiandrogens should be combined with an OCP in women in child bearing age as antiandrogens are teratogenic. Photo-epilation or electrolysis is mostly needed in order to reduce the amount of hair. Multiple treatments are needed. Hair reduction with each session with photo-epilation is estimated to 15% to 30%. Medical therapy and laser or IPL should be combined for best result.

Keywords: Hirsutism; PCOS; Impaired QoL; Ferriman-Gallwey scale; Medical treatment; Photo-epilation

Abbreviations: PCOS: Polycystic Ovary Syndrome; F-G scale: Ferriman and Gallwey Scale; HAIR-AN: Hyperandrogenism Insulin Resistance, Acne, Obesity and Acanthosis Nigricans; SAHA: Seborrhea, Acne, Hirsutism and Acanthosis Nigricans; CAH: Congenital Adrenal Hyperplasia; NCAH: Non-Classical Congenital Adrenal Hyperplasia; CS: Cushing's syndrome; USG: Ultrasound; PRL: Prolactin; T: Testosterone; SHBG: Sex Hormone Binding Globulin; DHEAS: Dehydroepiandrosteronsulfat; 17-OHP: 17-hydroxyprogesterone; 11-S: 11-deoxycortisol; fT4: Free Thyroxine; TSH: Thyroid Stimulating Hormone; IGF1: Insuline like Growth Factor; RIA: Radioimmunoassay; LH: Luteinizing Hormone; FSH: Follicle Stimulated Hormone; ACTH: Adrenocorticotropic Hormone; OCP: Oral Contraceptives; EE: Ethinyl Estradiol; 5αR: 5α-reductase; DHT: Dihydrotestosterone; CPA: Cyproterone Acetate; IPL: Intense Pulse Light; GnRHa: Gonadotropic-Releasing Hormone Analogs

Introduction

A patient story *"It has affected my life a lot. I have been embarrassed over myself as a person….. It is not normal for a woman to have hair in the face. I have avoided social activities with friends and made excuses not to attend…..Now it is easier the face is better, I have got a diagnosis and I have got help. I have told my friends now. It is easier … for you do something about it. Because it is more like a problem [that can be treated] I think".*

Hirsutism is a common endocrine disease among women and effects 5 to 15% [1-5]. It is excessive terminal hair in a male pattern distribution, caused by elevated androgen exposure to the hair follicles [2,6-8]. Approximately 5 million hair follicles cover the body [9]. Androgens are the most significant hormones in the hair growth modulation and are involved in keratinization, prolongation of the anagen phase and the stimulation of the transformation of vellus hairs into terminal hairs in androgen dependent areas. The presence of substantial numbers of terminal hairs over the chin, cheek, lower face and sideburns indicates androgen excess [10]. The most common cause of hirsutism is PCOS and is seen in 70% of hirsute women [11]. There are some evidence of familial aggregation of women with PCOS, hyperandrogenism and metabolic alterations [12]. Idiopathic hirsutism is considered in 10-15% [13] and is defined as normal ovulatory cycles, presence of normal ovarian morphology and a normal biochemical state [14]. It has mostly been considered as an ethnic or a genetic cause [15]. However, nearly 40% of women who are considered to have idiopathic hirsutism, and with a history of "regular" cycles are in fact oligo-or anovulatory, according to Azziz [16]. In Idiopathic hyperandrogenemia there has not been possible to establish the cause of hirsutism and hyperandrogenemia in spite of a thorough investigation [17,18]. The most common method used for assessment of hirsutism is the modified Ferriman and Gallwey scale [19,20]. Nine body areas are sensitive for androgens; each is scored from 0-4 and then summed to get a total hair growth score. The maximal total score is 36. A score of 6-8 is usually set as a cut-off score for hirsutism, 8 to 15 are considered as moderate hirsutismand a score above 15 as severe hirsutism [2,4].

Modified Ferriman Gallwey scale for assessment of hairiness

The Ferriman Gallwey scoring system is used to score the degree of excess body hair in women. Nine body areas are included (lower arms and lower legs are not included). Each body area is scored. The score begins from 0 (no excessive terminal hair growth) to 4 (extensive terminal hair growth). The scores from each body are added. The maximal total score is 36. A modified score of 6 to 8 or more indicates hirsutism.

There are ethnic variations in hair growth patterns [21], thus Asian women with PCOS tend to have less body and facial hair than European and Maori women with PCOS [22,23].

Rare causes of hirsutism are: HAIR-AN (hyperandrogenism, insulin resistance, acne, obesity and acanthosis nigricans), SAHA (seborrhea, acne, hirsutism and acanthosis nigricans) [24], Congenital adrenal hyperplasia (CAH), [25] and the non-classical congenital adrenal hyperplasia (NCAH), both are caused by 21-hydroxylase (21-OH) deficiency or androgen-secreting tumours in the ovaries or adrenal glands.

Hirsutism influences psychological well-being negatively, with social fears, anxiety and psychotic symptoms [26] and is described as a life sorrow [27]. Anxiety and depression are common in women with hirsutism [28-30]. Hair in the face is considered most troublesome and the higher the level of hair growth, the worse the quality of life [27,28]. Treatment that reduce hair, for instance with laser, improve quality of life [31,32].

Hirsutism must be differentiated from hypertrichosis, which is excessive hair growth on androgen-independent body areas, either localized or generalized [33,34]. It is mostly genetic or ethnic with no pathological background [35], but thyroid dysfunction, metabolic disorders, anorexia nervosa or drug related causes must be ruled out [33]. The most common medications causing hypertrichosis are Ciclosporine and Glucocorticoids [11].

Diagnosis of Hirsutism

A medical history should include: menstrual history, onset and progression of hairiness, weight gain, on-going or previous treatments and family history of hyperandrogenism. In adult women a cycle length over 35 days could be a sign of oligomenorrhea [10]. Androgen-secreting tumors in the ovaries or in the adrenal glands are very rare, but should not be over locked. Important signs are rapid onset and progression of virilization, high serum testosterone level. An abdominal or pelvic mass could sometimes be palpated [33]. A computed tomography or Magnetic Resonance Imaging of the pelvis should be done if there are suspicions of a tumorous cause to the virilization. Acromegaly, hyperprolactinemias and Cushing's syndrome (CS) can also cause hirsutism and should be ruled out. A routine screening for CS in patients with a referral diagnosis of hirsutism is not required according to Karaca et al. [36]. They recommend against routine testing for CS in patients with hirsutism if the patient does not have accompanying clinical stigmata of hypercortisolism. A clinical examination should include: assessment of hairiness, a check-up for other cutaneous signs of hyperandrogenism (acne, seborrhea, acanthosis nigricans and hair loss). Height, weight and blood pressure should be recorded. Ovarian morphology is mostly assessed by transvaginal ultrasound in order to calculate the number of follicles [10,37]. The ultrasound (USG) diagnosis of polycystic ovaries is defined as the presence of ten or more cysts 2-10 mm in diameter arranged around a dense stroma or scattered throughout an increased amount of stroma. Many women with PCOS are at risk of metabolic syndrome thus a check for lipid profile, blood pressure and a glucose test is warranted.

Laboratory testing

A basal laboratory test panel for women with hirsutism could often include prolactin (PRL), total testosterone, sex hormone binding globulin (SHBG), Dehydroepiandrosteronsulfat (DHEAS), androstenedione, 17-hydroxyprogesterone (17-OHP), 11-deoxycortisol (11-S), cortisol, free thyroxine (fT4) and TSH, and IGF1 levels. Laboratory testing of androgens in women with mild hirsutism is controversial, as some experts recommend against testing of s-testosterone (T) [38] and other recommend at least one determination of serum androgen levels before starting treatment. Free (T) levels are more sensitive than the measurement of total T to establish androgen excess. T measurements require equilibrium dialysis techniques by the laboratory, if a direct analogue radioimmunoassay (RIA) that could give an inaccurate level of the free-T assay. In that case it is better to use a calculated free T which has a good concordance and correlation with free T as measured by equilibrium [10]. There is also a significant variability between different assays and poor precision with all assays at low testosterone levels [39]. Hyperandrogenemia could be defined as increased serum testosterone, androstenedione, and/or DHEAS levels [36].

Sex hormone-binding globulin (SHBG) is often lowered in women with PCOS and obesity. Patients with PCOS often have elevated free serum testosterone with increased luteinizing hormone (LH) and lowered follicle-stimulated hormone (FSH) (FSH/LH=1:2 or 1:3) [11]. Somatomedin C and prolactin could be taken to rule out acromegaly [38,40] and (DHEAS) to rule out adrenal origin. Serum 17-OHP is taken to rule of CAH or NCAH. PCOS and NCAH have clinical and laboratory similarities, thus an ACTH (Adrenocorticotropic Hormone) stimulation test could be needed to differentiate between these syndromes [41] (Table 1).

Treatment

Medical treatment

The aim of medical treatment of hirsutism is to correct the hormonal imbalance and thereby stop further progress of hairiness. Any medical treatment must continue at least 6 months for an evaluation of effect and about 9 months to become maximal. That is because of the long hair-growth cycle.

Oral contraceptives

Oral contraceptives (OCP) are recommended as first line treatment. It often contains a synthetic estrogen ethinyl estradiol (EE) in combination with a progestin. The effect of OCPs is probably by stimulating the production of SHBG from the liver, thereby increasing the binding capacity of androgens in serum, suppression of LH secretion and therefore androgen secretion [10]. OCPs can also reduce the risk for endometrial cancer in women with PCOS and menstrual irregularities [42]. A non-androgenic progestin (drospirenone, dioenogest or cyproterone) is preferable [11]. Drospirenone is derived from spironolactone thus it has both anti-androgen and mineralocorticoid properties, blocks ovarian steroid production, peripheral androgen receptors in the dermis and pilosebaceous units and reduce adrenal androgen synthesis [43]. Although OCPs are considered as first-line therapy in PCOS, there are some potential side effects as increased risk of thromboembolism, stroke, myocardial infarction, metabolic side effects and breast cancer. The metabolic side effects are greater for more androgenic progestins and the risk of thromboembolism is higher with non-androgenic progestins [44,45].

Table 1: Important hormones in hirsutism

Testosterone	is mostly bound to SHBG (80%) and albumin (19%) in the circulation
	Testosterone/SHBG is an indirect measure of the biologic active part
	Testosterone is produced by the adrenal (25%), by the ovaries (25%) and from the fat tissue (50%)
	Testosterone is converted by 5α reductase to the more potent Dihyrotestosterone (DHT) in the skin and the liver in women and also in prostate in men
Androstenedione	Androstenedione is produced in the ovaries and in the adrenal glands, could be converted into testosterone in the fat tissue
DHEAS	DHEAS is normally produced in the adrenal glands. Higher levels than normal could be found in women with PCOS
s-17-OH-progesterone	An important hormone produced by the adrenal glands and gonads. The body uses 17-OH progesterone and the enzyme 21-Hydroxylase (21-OHD) to produce cortisol and aldosterone. In the absence of enzymes needed, testosterone and DHT are produced instead. 1/10000 new born have the disease congenital adrenal hyperplasia (CAH)

Antiandrogens

The mechanistic basis of anti-androgen therapy is for finasteride to inhibit 5α-reductase (5αR) to prevent the conversion of T to the more potent 5α-dihydrotestosterone (DHT) or to be a competitive antagonist of the androgen receptor (spironolactone, cyproterone acetate, flutamide) [10]. Antiandrogens may cause menstrual disturbances (i.e. spironolactone), have a teratogenic potential and must therefore be combined with adequate contraception. OCP is often combined with antiandrogens for additional effect. If hormonal contraception is contraindicated, for instance in women at risk for thrombophilia or in women older than 35 and heavy smokers, an intrauterine device must be used [5]. Antiandrogens for hirsutism treatment in Sweden are used off-label with the exception of cyproteronacetat.

Spironolactone is considered as the first-line antiandrogen [14]. It is well tolerated, have mild side effects and as effective as many other pharmacological options [34]. It exhibits dose-dependent competitive inhibition of the androgen receptor as well as inhibition of 5α reductase activity in the skin [46], which makes it useful for both hirsutism caused by hyperandrogenism and "idiopatic" hirsutism. Effective doses are 100-200 mg a day, divided into a two dose regime. Potential side effects are postural hypotension, increased diuresis and dizziness, menstrual irregularities and rarely hyperkalemia. To minimize side effects, it is advisable to start with a lower dose the first two weeks. Electrolytes should be checked after sixth week. If the electrolytes are normal it is sufficient to check them twice a year. The menstrual irregularities are dose-dependent. An OCP could be used concomitantly as menstrual cycle regulation. In addition OCPs and Spironolactone have complementary anti-androgen actions [11]. If given during pregnancy there is the danger of fetal male pseudohermaphroditism [38]. Thus spironolactone should not be given to a pregnant women or a woman who want to get pregnant.

Cyproterone acetate (CPA) is a progestogenic compound with anti-androgen activity. It is indicated for severe hirsutism in women. The main effect is inhibition of the androgen receptor. Doses of 50–100 mg/d of CPA are often prescribed until the maximal effect is obtained, and then lower doses (such as 5 mg/d) are prescribed for maintenance. CPA is mostly combined with an OCP. Side effects are menstrual irregularities, liver functional abnormalities, weight gain and depression. Weight gain and depression are common causes for patients to stop treatment. CPA is available in a lower dose (2 mg) in combination with ethinyl estradiol (EE), under the brand name of Diane and is more tolerable.

Flutamide inhibits the androgen receptor and reduces the synthesis of androgens. In clinical practice it is used in doses from 62.5 mg to 500 mg [47]. The most feared side effects are hepatic toxicity and liver failure. Flutamide has not been superior to spironolactone 100 mg in comparing studies [48-50].

Bicalutamide, indicated for prostate cancer, is a non- steroidal pure anti-androgen. It has been used in half the dose for women with hirsutism due to PCOS [47]. It is however not recommended in Sweden, because of its potential side effects and has not been proven to be superior to spironolactone.

Enzyme inhibitors

Finasteride inhibits the peripheral conversion of testosterone to Dihydrotestosterone (DHT), by inhibition of type II 5 alpha reductase and is used in doses from 1-7.5 mg [34,51].

Eflornithine as a local preparation is approved for facial hairiness. It inhibits ornithine decarboxylase in the hair follicle, thereby impeding formation of a polyamine critical to regulating cellular growth and differentiation in the hair follicle which results in thinner, shorter, less pigmented hair and reduced speed of hair growth.

The cream should be applied twice a day. The effect is seen after 8-10 weeks in about 70% of the treated women [34,40,51]. A reduction of hair mass by 26% and a 23% reduction in hair length could be expected. There is an additive effect in combination with laser or IPL by reducing hair regrowth between laser sessions [52]. It can also be used as an adjuvant to pharmacotherapy of hirsutism [53].

The treatment has to be continuous as the hair growth returns back to baseline in 8-10 weeks if treatment is discontinued. Side effects are not common, but stinging, irritation and contact dermatitis from the preservatives could be seen. The combination of OCP and antiandrogens is proven to be more effective in the treatment of hirsutism. A systematic review showed that OCP+flutamide or OCP+spironolactone or OCP+finasteride were superior to OCP monotherapy [5] and a meta-analysis of three trials got the same results [54].

Insulin-lowering drugs

Examples of insulin-lowering drugs are: *Metformin, pioglitazone,* Reducing insulin levels pharmacologically attenuates both hyperinsulinemia and thereby hyperandrogenemia. The opinion of insulin-lowering drugs in managing hirsutism without hyperinsulinemia has been conflicting. The extent to which these agents improve hirsutism remains unclear. Metformin that is the most used insulin-lowering drug in the treatment of hirsutism has been inferior to both spironolactone and flutamide [55]. Metformin has been used in adolescent girls with PCOS either as first-line monotherapy or in combination with OCPs and anti-androgens. It has also been used to prevent or delay the progression to PCOS in high-risk prepubertal girls [10]. Metformin has been compared with placebo in eight studies, in neither of the studies there was efficacy on hirsutism [56]. Thus insulin-lowering drugs should only be used in case of concomitant diabetes [38].

Glucocorticoids

Glucocorticoids, suppress the adrenal glands and thereby the adrenal androgens, but is restricted to special conditions such as infertility due to anovulation in women with NCAH [38].

Gonadotropic-releasing hormone analogs (GnRHa)

GnRHA is not recommended for hirsutism as there is insufficient evidence for efficacy in the treatment of hirsutism [1,38,47].

Epilation

Physical and Chemical Epilation

Most women use some home based treatments, such as shaving, electric epilating, cold or hot waxes or chemical epilation. These methods are cheap and easy to use, but are often associated with some skin irritation and folliculitis. To minimize side effects, one could give the patients some tips and tricks, such as using a clean shaving blade, to swab with gauze soaked with a weak boric acid solution and to use a hydrocortisone cream to minimize irritation after epilation.

Electro-epilation (Electrolysis)

An epilation probe is introduced into the hair follicle and destroys the follicle by galvanic electrolysis (direct current) or by thermolysis (high-frequency alternating current). The results are very operator-dependent. The regrowth rate is about 40% [34]. It is however the best method for gray hair.

Photo epilation

Hormonal therapy can stop further progress of the disorder, but it has only modest effects in reversing the hair growth. In order to reduce the amount of hair, photo epilation or electrolysis is needed. On the other

hand hair removals with lasers or IPL are much less effective in female patients suffering from Polycystic Ovarian Syndrome (PCOS) without hormonal thereby. Women with high androgen levels and elevated LH: FSH ratios require more treatment sessions than women with lover levels [57].

Lasers for hair removal are: Long pulsed Ruby laser (694), long-pulsed Alexandrite (755 nm), long-pulsed Nd:YAG (1064 nm) and long-pulsed Diode (800-810 nm). Long pulsed ruby lasers (694) were the first devices on the market for hair removals and resulted in long term hair reduction [58]. Intense Pulse Light (IPL) emits polychromatic non-coherent light with wave-lengths from 400-1400 nm. For hair removal a filter that filters the wave-lengths below 525-550 nm is often used [59].

The laser light is transferred into heat when it is absorbed by a chromophore, thus destroying the target by thermal damage without destroying adjacent tissues, a process called selective photothermolyis. In treatment of hirsutism with lasers or IPL, the goals are to destroy the hair follicle and to reduce the hair shaft caliber.

For hair removal melanin is the chromophore. Melanin absorbs light in the red and infrared range of the electromagnetic spectrum (600-1200 nm). The hair follicle itself contains no melanin. The target is in the hair and in the hair bulb.

The best results are obtained if hairs in the anagen (growing) phase are treated. Hairs in the other (resting) phases cannot be treated. Therefore treatment with lasers or IPL must be scheduled with appropriate treatment intervals.

The pulse width plays an important role in determining selective photothermolysis [60]. The duration of the pulse has to be shorter than the thermal relaxation time of the hair follicle, which in this case, is the time it takes for the heated hair follicle to cool half its peak temperature in order to minimize collateral thermal damage [9,52,61]. Fluence and pulse duration together influence the amount of heat absorbed in the target. To determine the thickness of the hair that should be removed is important in order to choose the right settings (Figure 1).

How to Choose Device for Hair Removal?

Today there are no devices that give permanent hair removal, however long-term reduction is possible to achieve. Multiple treatments are needed and with each session it is estimated that 15% to 30% of hairs are removed [62]. The long-pulsed alexandrite can be safely used in Fitzpatric skin phototypes I-III or even IV [63,64] and have long-term efficacy (12 months) ranges from 78% to 85% [65,66]. Several IPL:s has default settings for dark skin and separate hand pieces as well. Diode laser has been reported to reduce hair count with 22% to 59% [61,67-72]. Alexandrite and diode lasers are said to be slightly more efficacious than IPL in some studies but not to the point of statistical significance [53].

Other studies have found lasers and IPL equally effective [59,73]. A prospective randomized intrapatient, right-left assessor-blinded study compared Nd:YAG *vs* IPL for hair removal. There was significant better hair reduction after the first session on the Nd:YAG laser treated side. On the IPL treated side the hair reduction became significant after the third treatment. The patient satisfaction scores were higher with the IPL because of lower levels of side effects after treatment (pain, edema and burning sensation) [74]. If IPL is used for hair removal it should have a dual filter system, i.e., also a water filter that filters wave length above 900 nm in order to protect the skin from being burned (Table 2, Figure 2).

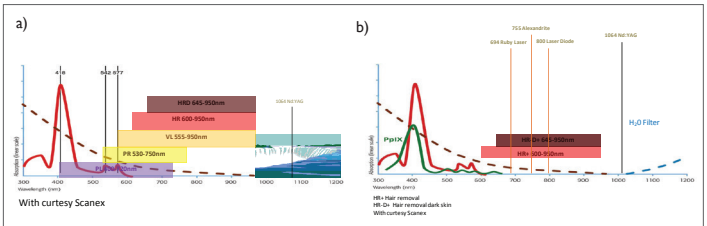

Figure 1a: IPL light with dual filters
While other equipment just filter light at the left end of the absorption curve, the Ellipse can also filter light towards the right, where water absorption occurs in the skin. (Patented). The target chromophore will therefore absorb the majority of light radiated without damaging the surrounding tissue.
b: Wavelengths in hair removal lasers and IPL.
Penetration is also dependent on the pulse type and duration, in other words, the time it takes for light to penetrate the skin. Once the correct applicator is selected, we adjust λ to the target chromophore. It uses the same principles as that of the Laser but with the versatility of the IPL. By using Ellipse filters and applying the appropriate pulse to the lesion, one laser can perform the same treatments that would normally require the use of several specific laser.

Weight Reduction

Weight reduction in women with hirsutism and obesitas is important, even if it is not proven that it leads to hair reduction. It decreases serum-insulin, ovarian androgen production and the conversion of androstendione to testosterone and increases sex hormone-binding globulin production [75,76]. It reduces the cardiovascular risk and could prevent diabetes. A plan for physical exercise should be included in the strategy for weight reduction. Referral to a dietitian may be needed to get a "diet plan".

Conclusion

- Hirsutism is a symptom of underlying androgen excess or increased sensitivity to androgens in the hair follicles. It causes profound stress in women and negative impact on quality of life.
- A multidisciplinary approach is needed.
- To inform the patient about the diagnos and to offer treatment is crucial and could helpt the patient to cope with the situation.
- Basal laboratory tests before treatment is advisable (s-testosterone, SHBG, DHEAS, 17-OHP, FSH, LH, s-prolactin, TSH). Further investigations could be needed.

Table 2: Treatment intervals

Area	Interval after first treatment	Intervals there after
Upper lip	6 weeks	6-8 weeks
Chin and cheeks	6 weeks	8 weeks
Ears and eyebrows	6 weeks	8 weeks
Underarms	8 weeks	10 weeks
Bikin areas	8 weeks	10 weeks
Arms	10 weeks	12 weeks
Legs	12 weeks	12-14 weeks

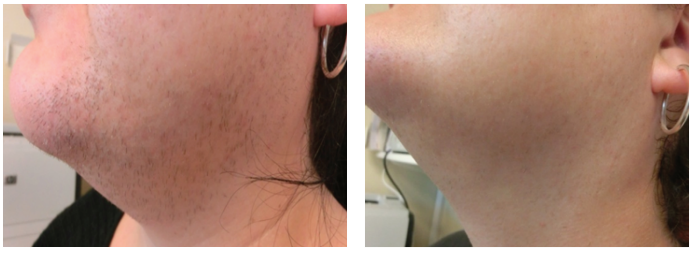

Figure 2: A woman diagnosed with PCOS after 6 treatments with IPL and medication with spironolactone and OCP. Before her 7th treatment.

- An ultrasound should be performed, of the ovaries if there are menstrual irregularities.
- It is important to give the patient reasonable expectations.
- Laser and IPL give long-lasting hair reduction but not complete and persistent hair removal.
- Laser or IPL should be combined with topical Eflornithine it is tolerated by the skin.
- Spironolactone is the first choice if an antiandrogen should be used.
- Antiandrogens should be combined with OCP in women in childbearing age.
- Treatment should not give serious side effects as hirsutism per se is a benign disease.

Ethical Considerations

The patient story is from material approved by the ethics committee of Orebro University Hospital (diary no. 288/02).

Photos are published with the patient's consent. The photos and the patient story are not from the same woman.

References

1. Azziz R (2003) The evaluation and management of hirsutism. Obstet Gynecol 101: 995-1007.
2. Rosenfield RL (2005) Clinical practice. Hirsutism. N Engl J Med 353: 2578-2588.
3. Mofid A, Seyyed Alinaghi SA, Zandieh S, Yazdani T (2008) Hirsutism. Int J Clin Pract 62: 433-443.
4. Azziz RE, Carmina E, Sawaya ME (2000) Idiopathic hirsutism. Endocrine Reviews 21: 347-62.
5. Escobar-Morreale HF, Carmina E, Dewailly D, Gambineri A, Kelestimur F, et al. (2012) Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update 18: 146-170.
6. Thiboutot DM, Knaggs H, Gilliland K, Hagari S (1997) Activity of type 1 5 alpha-reductase is greater in the follicular infrainfundibulum compared with the epidermis. Br J Dermatol 136: 166-171.
7. Randall VA (2008) Androgens and hair growth. Dermatol Ther 21: 314-328.
8. Ekbäck MP, Lindberg M, Benzein E, Årestedt K (2014) Social support: an important factor for quality of life in women with hirsutism. Health Qual Life Outcomes 12: 183.
9. Sanchez LA, Perez M, Azziz R (2002) Laser hair reduction in the hirsute patient: a critical assessment. Hum Reprod Update 8: 169-181.
10. Goodman NF, Cobin RH, Futterweit W, Glueck JS, Legro RS, et al. (2015) American Association of Clinical Endocrinologists, American College of Endocrinology, And Androgen Excess and Pcos Society Disease State Clinical Review: Guide to The Best Practices In The Evaluation And Treatment of Polycystic Ovary Syndrome--Part 1. Endocr Pract 21: 1291-1300.
11. Brodell LA, Mercurio MG (2010) Hirsutism: Diagnosis and management. Gend Med 7: 79-87.
12. Franks S, McCarthy M (2004) Genetics of ovarian disorders: polycystic ovary syndrome. Rev Endocr Metab Disord 5: 69-76.
13. Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, et al. (2004) Androgen excess in women: experience with over 1000 consecutive patients. J Clin Endocrinol Metab 89: 453-462.
14. Markovski, Hall J, Jin M, Laubscher T, Regier L (2012) Approach to the management of idiopathic hirsutism. Can Fam Physician 58: 173-177.
15. Dierickx C, Alora MB, Dover JS (1999) A clinical overview of hair removal using lasers and light sources. Dermatol Clin 17: 357-366.
16. Azziz R, Waggoner WT, Ochoa T, Knochenhauer ES, Boots LR (1998) Idiopathic hirsutism: an uncommon cause of hirsutism in Alabama. Fertil Steril 70: 274-278.
17. Carmina E (2006) The spectrum of androgen excess disorders. Fertil Steril 85: 1582-1585.
18. Unluhizarci K, Gokce C, Atmaca H, Bayram F, Kelestimur F (2004) A detailed investigation of hirsutism in a Turkish population: idiopathic hyperandrogenemia as a perplexing issue. Exp Clin Endocrinol Diabetes 112: 504-509.
19. Ferriman D, Gallwey JD (1961) Clinical assessment of body hair growth in women. J Clin Endocrinol Metab 21: 1440-1447.
20. Hatch R, Rosenfield RL, Kim MH, Tredway D (1981) Hirsutism: implications, etiology, and management. Am J Obstet Gynecol 140: 815-830.
21. Lee HJ, Ha SJ, Lee JH, Kim JW, Kim HO, et al. (2002) Hair counts from scalp biopsy specimens in Asians. J Am Acad Dermatol 46: 218-221.
22. Williamson K, Gunn AJ, Johnson N, Milsom SR (2001) The impact of ethnicity on the presentation of polycystic ovarian syndrome. Aust N Z J Obstet Gynaecol 41: 202-206.
23. Kim JJ, Chae SJ, Choi YM, Hwang SS, Hwang KR, et al. (2011) Assessment of hirsutism among Korean women: results of a randomly selected sample of women seeking pre-employment physical check-up. Hum Reprod 26: 214-220.
24. Rager KM, Omar HA (2006) Androgen excess disorders in women: the severe insulin-resistant hyperandrogenic syndrome, HAIR-AN. Scientific World Journal 24: 116-121.
25. Chen W, Obermayer-Pietsch B, Hong JB, Melnik BC, Yamasaki O, et al. (2011) Acne-associated syndromes: models for better understanding of acne pathogenesis. J Eur Acad Dermatol Venereol 25: 637-646.
26. Sonino N, Fava GA, Mani E, Belluardo P, Boscaro M (1993) Quality of life of hirsute women. Postgrad Med J 69: 186-189.
27. Ekback M, Wijma K, Benzein E (2009) "It is always on my mind": women's experiences of their bodies when living with hirsutism. Health Care Women Int 30: 358-372.
28. Lipton MG, Sherr L, Elford J, Rustin MH, Clayton WJ (2006) Women living with facial hair: the psychological and behavioral burden. J Psychosom Res 61: 161-168.
29. Drosdzol A, Skrzypulec V, Plinta R (2010) Quality of life, mental health and self-esteem in hirsute adolescent females. J Psychosom Obstet Gynaecol 31: 168-175.
30. Ekbäck MP, Lindberg M, Benzein E, Arestedt K (2013) Health-related Quality of life, depression and anxiety correlate to the degree of hirsutism. Dermatology 227: 278-284.
31. Loo WJ, Lanigan SW (2002) Laser treatment improves quality of life of hirsute females. Clin Exp Dermatol 27: 439-441.
32. Mc Gill DJ, Hutchison C, Mc Kenzie E, Mc Sherry E, Mackay IR (2007) Laser hair removal in women with polycystic ovary syndrome. J Plast Reconstr Aesthet Surg 60: 426-431.
33. Bode D, Seehusen DA, Baird D (2012) Hirsutism in women. Am Fam Physician 85: 373-380.
34. Blume-Peytavi U (2013) How to diagnose and treat medically women with excessive hair. Dermatol Clin 31: 57-65.
35. Blume-Peytavi U (2011) An overview of unwanted female hair. Br J Dermatol 165: 19-23.
36. Karaca Z, Acmaz B, Acmaz G, Tanriverdi F, Unluhizarci K, et al. (2013) Routine screening for Cushing's syndrome is not required in patients presenting with hirsutism. Eur J Endocrinol 168: 379-384.

37. De Leo V, Musacchio MC, Cappelli V, Massaro MG, Morgante G, et al. (2016) Genetic, hormonal and metabolic aspects of PCOS: an update. Reprod Biol Endocrinol 14: 38.

38. Martin KA, Chang RJ, Ehrmann DA, Ibanez L, Lobo RA, et al. (2008) Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 93: 1105-1120.

39. Legro RS, Schlaff WD, Diamond MP, Coutifaris C, Casson PR, et al. (2010) Total testosterone assays in women with polycystic ovary syndrome: precision and correlation with hirsutism. J Clin Endocrinol Metab 95: 5305-5313.

40. Harrison S, Somani N, Bergfeld WF (2010) Update on the management of hirsutism. Cleve Clin J Med 77: 388-398.

41. Pignatelli D (2013) Non-classic adrenal hyperplasia due to the deficiency of 21-hydroxylase and its relation to polycystic ovarian syndrome. Front Horm Res 40: 158-170.

42. Dumesic DA, Lobo RA (2013) Cancer risk and PCOS. Steroids 78: 782-785.

43. Batukan C, Muderris II (2006) Efficacy of a new oral contraceptive containing drospirenone and ethinyl estradiol in the long-term treatment of hirsutism. Fertil Steril 85: 436-440.

44. Lakhani K, Prelevic GM, Seifalian AM, Atiomo WU, Hardiman P (2004) Polycystic ovary syndrome, diabetes and cardiovascular disease: risks and risk factors. J Obstet Gynaecol 24: 613-621.

45. Diamanti-Kandarakis, Baillargeon JP, Iuorno MJ, Jakubowicz DJ, Nestler JE (2003) A modern medical quandary: polycystic ovary syndrome, insulin resistance, and oral contraceptive pills. J Clin Endocrinol Metab 88: 1927-1932.

46. Brown J, Farquhar C, Lee O, Toomath R, Jepson RG (2009) Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Cochrane Database Syst Rev CD000194.

47. Blume-Peytavi U, Hahn S (2008) Medical treatment of hirsutism. Dermatol Ther 21: 329-339.

48. Andrade RJ, Lucena MI, Fernández MC, Suárez F, Montero JL, et al. (1999) Fulminant liver failure associated with flutamide therapy for hirsutism. Lancet 353: 983.

49. Moghetti P, Tosi F, Tosti A, Negri C, Misciali C, et al. (2000) Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. J Clin Endocrinol Metab 85: 89-94.

50. Osculati A, Castiglioni C (2006) Fatal liver complications with flutamide. Lancet 367: 1140-1141.

51. Loriaux DL (2012) An approach to the patient with hirsutism. J Clin Endocrinol Metab 97: 2957-2968.

52. Hamzavi I, Tan E, Shapiro J, Lui H (2007) A randomized bilateral vehicle-controlled study of eflornithine cream combined with laser treatment versus laser treatment alone for facial hirsutism in women. J Am Acad Dermatol 57: 54-59.

53. Somani N, Turvy D (2014) Hirsutism: an evidence-based treatment update. Am J Clin Dermatol 15: 247-266.

54. Swiglo BA, Cosma M, Flynn DN, Kurtz DM, Labella ML, et al. (2008) Clinical review: Antiandrogens for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. J Clin Endocrinol Metab 93: 1153-1160.

55. Cosma M, Swiglo BA, Flynn DN, Kurtz DM, Labella ML, et al. (2008) Clinical review: Insulin sensitizers for the treatment of hirsutism: a systematic review and metaanalyses of randomized controlled trials. J Clin Endocrinol Metab 93: 1135-1142.

56. Van Zuuren EJ, Fedorowicz Z (2016) Interventions for hirsutism excluding laser and photoepilation therapy alone: abridged Cochrane systematic review including GRADE assessments. Br J Dermatol 175: 45-61.

57. Karn D, K C S, Timalsina M, Gyawali P (2014) Hormonal profile and efficacy of long pulse Nd-YAG laser in treatment of hirsutism. J Nepal Health Res Counc 12: 59-62.

58. Grossman MC, Dierickx C, Farinelli W, Flotte T, Anderson RR (1996) Damage to hair follicles by normal-mode ruby laser pulses. J Am Acad Dermatol 35: 889-894.

59. Zandi S, Lui H (2013) Long-term removal of unwanted hair using light. Dermatol Clin 31: 179-191.

60. Anderson RR, Parrish JA (1983) Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. Science 220: 524-527.

61. Gan SD, Graber EM (2013) Laser hair removal: a review. Dermatol Surg 39: 823-838.

62. Ibrahimi OA, Avram MM, Hanke CW, Kilmer SL, Anderson RR (2011) Laser hair removal. Dermatol Ther 24: 94-107.

63. Wanner M (2005) Laser hair removal. Dermatol Ther 18: 209-216.

64. Davoudi SM, Behnia F, Gorouhi F, Keshavarz S, Nassiri Kashani M, et al. (2008) Comparison of long-pulsed alexandrite and Nd:YAG lasers, individually and in combination, for leg hair reduction: an assessor-blinded, randomized trial with 18 months of follow-up. Arch Dermatol 144: 1323-1327.

65. Eremia S, Li C, Newman N (2001) Laser hair removal with alexandrite versus diode laser using four treatment sessions: 1-year results. Dermatol Surg 27: 925-929.

66. Lloyd JR, Mirkov M (2000) Long-term evaluation of the long-pulsed alexandrite laser for the removal of bikini hair at shortened treatment intervals. Dermatol Surg 26: 633-637.

67. Lou WW, Quintana AT, Geronemus RG, Grossman MC (2000) Prospective study of hair reduction by diode laser (800 nm) with long-term follow-up. Dermatol Surg 26: 428-432.

68. Baugh WP, Trafeli JP, Barnette DJ Jr, Ross EV (2001) Hair reduction using a scanning 800 nm diode laser. Dermatol Surg 27: 358-364.

69. Campos VB, Dierickx CC, Farinelli WA, Lin TY, Manuskiatti W, et al. (2000) Hair removal with an 800-nm pulsed diode laser. J Am Acad Dermatol 43: 442-447.

70. Fiskerstrand EJ, Svaasand LO, Nelson JS (2003) Hair removal with long pulsed diode lasers: a comparison between two systems with different pulse structures. Lasers Surg Med 32: 399-404.

71. Rogachefsky AS, Silapunt S, Goldberg DJ (2002) Evaluation of a new super-long-pulsed 810 nm diode laser for the removal of unwanted hair: the concept of thermal damage time. Dermatol Surg 28: 410-414.

72. Sadighha A, Mohaghegh Zahed G (2009) Meta-analysis of hair removal laser trials. Lasers Med Sci 24: 21-25.

73. Haak CS, Nymann P, Pedersen AT, Clausen HV, Feldt Rasmussen U, et al. (2010) Hair removal in hirsute women with normal testosterone levels: a randomized controlled trial of long-pulsed diode laser vs. intense pulsed light. Br J Dermatol 163: 1007-1013.

74. Szima GZ, Janka EA, Kovács A, Bortély B, Bodnár E, et al. (2017) Comparison of hair removal efficacy and side effect of neodymium:Yttrium-aluminum-garnet laser and intense pulsed light systems (18-month follow-up). J Cosmet Dermatol.

75. Panidis D, Tziomalos K, Papadakis E, Vosnakis C, Chatzis P, et al. (2013) Lifestyle intervention and anti-obesity therapies in the polycystic ovary syndrome: impact on metabolism and fertility. Endocrine 44: 583-590.

76. Moran LJ, Hutchison SK, Norman RJ, Teede HJ (2011) Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev CD007506.