

Review Article

Etiology and Treatment of Hirsutism

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Abstract

Hirsutism, excessive hair growth in women in a male pattern distribution, is an international issue and approximately 5 to 15% of the general population of women is reported to be hirsute. It causes profound stress in women. As hirsutism is a symptom and not a disease it is important to find the underlying cause. Polycystic ovary syndrome is the most common cause but other not so common endocrinology disorders must be excluded. Mild hirsutism could be seen in a woman with normal menses and normal androgen levels (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 hirsute state. The aim of the medical treatment is to correct the hormonal imbalance and 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 as antiandrogens are teratogenic. Photo-epilation or electrolysis is mostly needed in order to reduce the amount of hair. Multiple treatments are required. 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

INTRODUCTION

Hirsutism in women is defined as excessive terminal hair distributed in a male pattern. It is caused by hair follicles being exposed to an elevated level of androgens [1-4]. The presence of substantial numbers of terminal hairs over the chin, neck, lower face and sideburns indicates androgen excess [5].

Hirsutism must be differentiated from hypertrichosis, which is excessive hair growth on androgen-independent body areas. This can be localised, for instance on the lower leg or lower arms or generalised over the whole body [6,7]. This is usually genetically determined and not pathological [8]. Some cases may be caused by thyroid dysfunction, metabolic disorders or anorexia nervosa [6]. Several drugs have been associated with hypertrichosis (for instance; acetazolamide, antipsychotic drugs, cyclosporine, glucocorticoids, methyl dopa, metoclopramide, phenytoin, penicillamine phenothiazines and reserpine) [9].

Approximately 5 million hair follicles cover the body. Hair follicles are mostly associated with sebaceous glands (i.e. forming the pilo-sebaceous unit) [10]. The hair growth has a three stage cycle: anagen phase (growth phase), catagen phase (involution phase) and telogen phase (resting phase) [11]. Several growth factors are involved in hair growth, for instance, insulin-like growth factor I and keratinocyte growth factor. An extended anagen stage and abnormal enlargement of the hair follicles lead to hirsutism. Genes are responsible for the difference in hair growth on the body [1,11,12]. Androgens are the most significant hormones in 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 [11].

Hirsutism is a common endocrine disease among women; approximately 5 to 15% of women are reported to be hirsute [1,13-16]. The higher prevalence of hirsutism reported in some studies may represent an overestimation caused by self-referral bias [16]. Hirsutism is a sign of increased androgen activity at the hair follicles either as a result of increased circulating levels of androgens or increased sensitivities of the hair follicles to normal circulating levels of androgens [17]. The areas most affected are the face and the lower abdomen [18]. The most common cause of hirsutism is polycystic ovary syndrome (PCOS), seen in 70% of hirsute women [9]. There is some evidence of familial aggregation in women with PCOS, [19]. The model of inheritance has not been fully defined. The candidate genes are those encoding for factors involved in the synthesis, transport, regulation and effects of androgens. Other candidate genes are those encoding for factors in insulin metabolism, genes coding for TNF- α , IL-6, IL-6 receptor or genes involved in folliculogenesis [20].

Hirsutism negatively influences psychological well-being, with resulting social fears, anxiety and psychotic symptoms [21] and is described as a life sorrow [22]. In addition the social norm of femininity today includes being totally free of body hair [23,24]. Anxiety and depression are common in women with hirsutism [25-27] and in women diagnosed with PCOS, it is rated as the second most important factor in determining quality of life [28]. Hair on the face is considered most troublesome and can

preoccupy a woman's minds [22,25] and be experienced as a betrayal of womanhood [29]. The greater the level of hair growth the worse the quality of life, measured by the Dermatology Life Quality Index (DLQI) and the EQ-index, Hair growth also lowers the level of self-perceived health status, measured by the EQ-VAS [27]. Jayprakasam found in a study of dermatological outpatients with 25 different skin diseases that only Bechet's disease resulted in a worse DLQI score than hirsutism [30]. Treatments that reduce hair growth, laser treatments for instance, improve quality of life [31,32].

ETIOLOGY AND PATHOPHYSIOLOGY OF HIRSUTISM

Polycystic ovary syndrome (PCOS)

PCOS is the most common cause of hirsutism [9], and it is seen in 70% of hirsute women. Most patients have the classic anovulatory form, but the ovulatory form is estimated to be present in 20% of PCOS patients [33]. According to the Rotterdam diagnostic criteria the PCOS diagnosis is determined if oligo/or anovulation, clinical and/or biochemical signs of hyperandrogenism and/or polycystic ovaries are found and other causes of hyperandrogenism are excluded (i.e. adrenal hyperplasia, androgen secreting tumors, Cushing's syndrome and Acromegaly). Clinical manifestations of PCOS are: hirsutism, obesity, insulin resistance, acne and cardiovascular complications [34]. Insulin receptors are present in the ovaries and insulin can bind to the Insulin Growth Factor (IGF). Insulin can then act as a co-gonadotropic and stimulate the androgen production in cooperation with Luteinizing Hormone (LH). Furthermore, insulin stimulates the synthesis of estrogen and progesterone, enhances ovarian growth and cystic formations, stimulates theca cell proliferation (where androgens are produced), activates the IGF-1 system and influences ovulation [20]. Intensive insulin therapy may enhance the development of PCOS in women with diabetes type I, according to Codner [35]. Lean women with idiopathic hirsutism have also shown to be more insulin resistant than healthy women [36].

Idiopathic hirsutism

It is considered in 10-15% of the cases [37]. They have normal ovulatory cycles and a normal biochemical state [38]. Mostly it has been considered as an ethnic or a genetic cause [39]. 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 [40]. Thus mild polycystic ovary syndrome seems to be more common than idiopathic hirsutism in women with hirsutism and "normal" ovulatory cycles [41]. Other causes of "idiopathic" hirsutism could be abnormalities in the androgen receptor, increased peripheral activity of 5-alpha reductase in the hair follicle [15] or mild to moderate abnormalities in the steroidogenesis in the adrenal gland, the ovary, or both [42]. Hirsutism is a sign of androgen excess; however the severity of hirsutism does not fully correlate to the magnitude of the androgen excess [41,43,44]. There is also a significant variability between different assays and poor precision with all assays at low testosterone levels [45]. Androgens are normally produced in women and the skin is

hormonally active and could convert androgens to more potent variants.

Rare causes

Rare causes of hirsutism are HAIR-AN (hyperandrogenism, insulin resistance, acne, obesity and acanthosis nigricans), SAHA (seborrhea, acne, hirsutism and acanthosis nigricans) [46], Congenital adrenal hyperplasia (CAH), an autosomal recessive inherited disorder, caused by an enzymatic defect in the biosynthetic pathway of cortisol and aldosterone [47] and the non-classical congenital adrenal hyperplasia (NCAH), both are caused by 21-hydroxylase (21-OH) deficiency. These diseases can be presented with premature pubarche, hirsutism in the prepubertal years and primary amenorrhea; however hirsutism could be the only sign of the disease [48]. Acromegaly hyperprolactinemia and Cushing's syndrome can also cause hirsutism. Androgen-secreting tumors in the ovaries or in the adrenal glands are very rare, but are important to diagnose. In these cases there is a rapid onset and progression of virilization.

Drugs

Drugs that could cause hirsutism are valproic acid, androgens and anabolic steroids and some progestins in oral contraceptives.

DIAGNOSIS OF HIRSUTISM

Medical history

A thorough medical history should include: menstrual history, onset and progression of hairiness, weight gain, on-going or previous treatments and family history of hyperandrogenism. There is an increasing evidence of familial aggregation of women with PCOS, hyperandrogenism and metabolic alterations [19]. In adult women a cycle length over 35 days could be a sign of oligomenorrhea [5].

Clinical examination

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 assessed by transvaginal ultrasound in order to calculate the number of follicles [5,20]. For young girls transabdominal ultrasounds may be used, even if that technique is less accurate in calculating small follicles [5]. Computer tomography or Magnetic Resonance of the pelvis could be done if there are suspicions of adrenal origin, or if more information is needed to rule out serious underlying causes.

It is important to rule out other causes of hirsutism such as Cushing's disease, acromegaly or a thyroid disorder [49]. High blood pressure could be a sign of Cushing's disease and is also a sign of cardiovascular risk. Many women with PCOS are at risk of metabolic syndrome and thus a check for that is warranted (lipid profile, blood pressure and a 2-h post 75-g oral glucose challenge to assess glucose tolerance).

Androgen-secreting tumors usually manifest with sudden onset and rapid progression of hirsutism and severe virilisation, in contrast to functional causes of hirsutism which have a pubertal onset and slower progression.

Laboratory testing

Laboratory testing of s-testosterone in women with mild hirsutism is controversial, as some experts recommend against testing [50] and others recommend at least one determination of serum androgen levels before starting treatment. Free testosterone levels are more sensitive than the measurement of total testosterone to establish androgen excess [5]. 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) [9]. Somatomedin C and prolactin are taken to rule out acromegaly [49,50]. DHEAS are taken to rule out adrenal origin (Table 1,2).

ASSESSMENT OF HAIRINESS

Subjective measurement

The most common method used is the visual scoring method, initially developed by Ferriman and Gallwey in 1961 [51]. This method has been modified by Hatch, Rosenfield, Kim and Tredway 1981 [52]. 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 and a score of 6-8 is usually

set as a cut-off score for hirsutism. A Ferriman-Gallwey score of 8 to 15 indicates moderate hirsutism and a score above 15 are considered as severe hirsutism [1,15]. The modified Ferriman-Gallwey score is the most widely used scale. One limitation is however its subjective nature [5]. Another limitation is that the sideburn not is included in the scale [52]. The measurement of terminal hair on the chin or the lower abdomen with a Ferriman-Gallwey score ≥ 2 can be used to estimate the amount of total body hair [53]. Bardin constructed a scale for grading of facial hirsutism. The Bardin scale also included the side burn. Each portion of the face involved (side burns, upper lip, chin) got a score of 1+. The maximum score was set to 4+ if the entire beard area was involved [54]. This scale has however not come in use.

Objective measurement

Objective methods for measuring hair growth are, for instance, photographic evaluations and microscopic measurements. However these methods have weaknesses as well, photographs may differ in colour and women must let their hair grow in order to be evaluated.

Ethnic differences

It is well known that there are ethnic variations in hair growth patterns [55]. Asian women tend to have less body and facial hair than European and Maori women [56]. The modified Ferriman-Gallwey scoring system does not account for ethnic differences, and there are no well-established race-specific normative ranges [57].

In a study by Carmina et al. seventy-five women with polycystic ovary syndrome participated. Twenty five women were from the United States, Italy and Japan respectively. Controls were ten women with normal ovulation and menstrual cycles. Hirsutism, obesity, and the presence of cystic ovaries were assessed, as were blood levels for estrogen, luteinizing hormone, testosterone, adrenal androgens, and insulin. Women from Japan were less obese ($p < 0.05$) and did not have hirsutism, although the percentage of cystic ovaries, levels of testosterone, adrenal androgens were comparable [58]. In a health survey in Seoul at the National University Hospital, 4550 premenopausal women, aged 18-40 were investigated as a part of a group physical check-up for their occupation. Of these women, 1448 women received routine cancer screening and gynecologic examinations according to their health check programs. From that group 1010 female accepted to participate in a study which aim was to investigate the degree and distribution of hair according to the modified Ferriman-Gallwey score and to define the cutoff value in Korean women. In addition, the associations between the modified Ferriman-Gallwey score and hormonal or metabolic markers were assessed. The result from the study was, that a score of six or greater represented hirsutism in a population of Korean women and there were significant associations between serum total T, SHBG and hemoglobin A1C [57] (Figure 1).

MEDICAL TREATMENT OF HIRSUTISM

The aim of medical treatment of hirsutism is to correct the hormonal imbalance and thereby stop further progress of hairiness and to reduce the amount of hair in order to improve the aesthetic appearance of the woman. Any medical treatment

Table 1: Treatment intervals.

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

Table 2:

Hormones	involved in hirsutism
Testosterone	In circulation mostly bound to SHBG (80%) and albumin (19%) Testosterone/SHBG is an indirect measure of the biologic active part Testosterone in the circulation is produced by the adrenal (25%), by the ovaries (25%) and from the fat tissue (50%) Testosterone is converted by 5 α reductase to the more potent Dehydrotestosterone (DHT)
Androstendion	Androstendion 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 absence of enzymes needed, testosterone and DHT are produced instead. 1/10 000 newborn have the disease congenital adrenal hyperplasia (CAH)

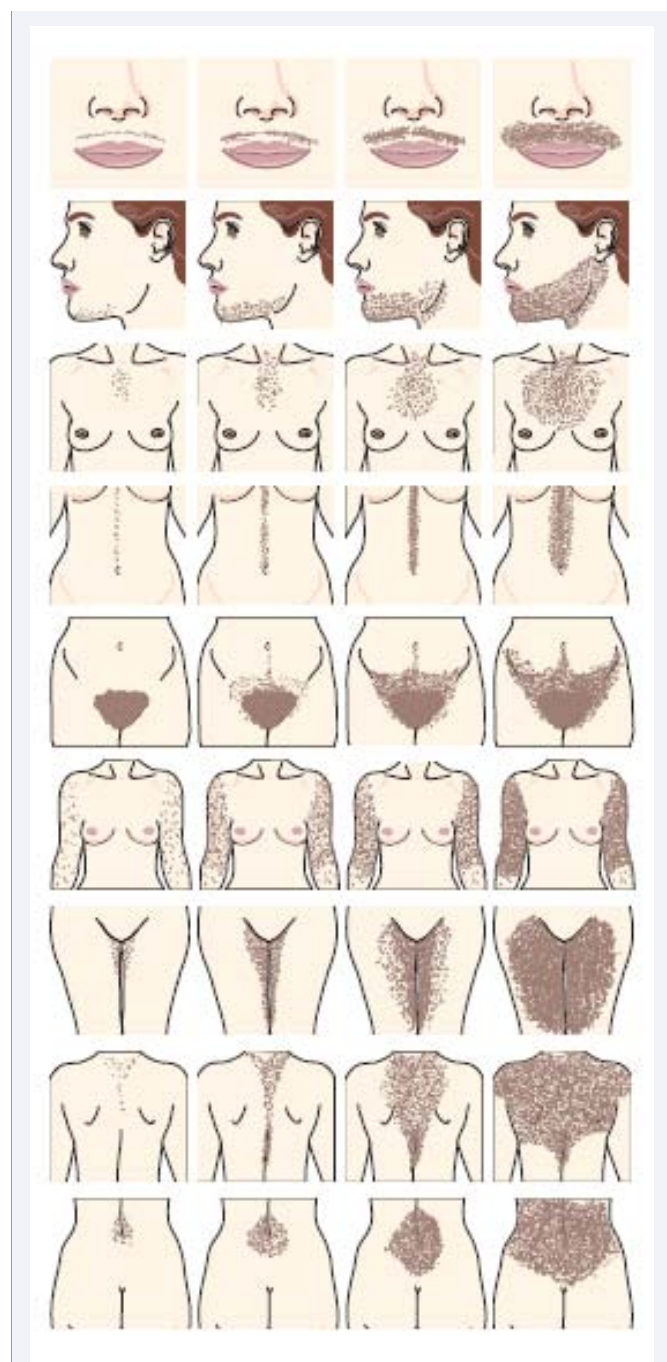


Figure 1

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 (OCP)

OCP are recommended as first line treatment. It contains a synthetic estrogen ethinyl estradiol (EE) in combination with a progestin. However the effectiveness on hair reduction is not convincing. According to Martin and co-workers it is not proven that OCPs reduce hairiness [50] and the American association of clinical endocrinologists/American College of endocrinology and

androgen excess (AACE/ACE) conclude that OCPs as monotherapy are not very effective in arresting hirsutism and should therefore be combined with an antiandrogen. It is more likely that OCPs attenuate hirsutism 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 [5]. OCPs can also reduce the risk for endometrial cancer in women with PCOS [59] and is therefore important in the treatment of women with PCOS and menstrual irregularities. A non-androgenic progestin (drospirenon, dienogest or cyproterone) is preferable regarding hirsutism [9]. Drospirenone is derived from spironolactone, thus it has both anti-androgen and mineralocorticoid properties. Drospirenone blocks ovarian steroid production, reducing adrenal androgen synthesis and blocking peripheral androgen receptors in the dermis and pilosebaceous units [60]. Although OCPs are considered as first-line therapy in PCOS, their use is controversial given the potential side effects. Potential side effects are increasing risk of thromboembolism, stroke, myocardial infarction, metabolic side effects and breast cancer. The metabolic side effects may be greater with more androgenic progestins and the risk of thromboembolism is greater with the non- androgenic progestins [61,62].

Antiandrogens

The mechanistic basis of anti-androgen therapy is for flutamide to inhibit 5α -reductase ($5\alpha R$) 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 [5]. All antiandrogens may cause menstrual disturbances or even amenorrhea when given alone, because of their strong progestin effects but they are not contraceptives. Thus all antiandrogens must be combined with adequate contraception as there is a teratogenic potential with these medications. If hormonal contraception is contraindicated, for instance in women at risk for thrombophilia or in women older than 35 and heavy smokers, contraception must be assured by use of an intrauterine device [16]. Antiandrogens for hirsutism treatment in Sweden are used off-label with the exception of cyproteronacetat.

Spironolactone: It is considered as the first-line antiandrogen by some researchers [38]. It is well tolerated and as effective as many other pharmacological options. It exhibits dose-dependent competitive inhibition of the androgen receptor as well as inhibition of 5α reductase activity in the skin [63]. It makes it useful for both hirsutism caused by hyperandrogenism and "idiopathic" hirsutism. Effective doses are 100-200mg a day, divided into a two dose regime. Spironolactone 100mg/day seems to be more effective in the treatment of hirsutism, due to hyperandrogenism, than low-dose cyproterone acetate 12.5mg/day (the first 10 days of cycle) and finasteride 5mg/day [7].

Side effects are postural hypotension, gastrointestinal side effects, increased diuresis and dizziness, menstrual irregularities and in rare cases hyperkalemia. It is advisable to start with a low dose of spironolactone the first two weeks to minimize symptomatic side effects (i.e. gastrointestinal, orthostatic reactions). Electrolyte levels and renal function should be checked before treatment start and then after sixth weeks. If the electrolyte

levels are normal, it is sufficient to check electrolyte levels twice a year. The menstrual irregularities are dose-dependent unless an OCP is used concomitantly. If given during pregnancy there is the danger of fetal male pseudohermaphroditism [50]. Thus spironolactone is contraindicated during pregnancy as the other antiandrogens. An OCP is mostly used concomitantly as menstrual cycle regulation. In addition OCPs and Spironolactone have complementary anti-androgen actions [9].

Cyproterone acetate (CPA): 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. CPA has a long half-life and is therefore administered in a sequential way 100mg for the first ten days and thereafter in a lower dose. CPA is mostly combined with an OCP.

Side effects are menstrual irregularities, liver functional abnormalities, weight gain and depression [64]. CPA is available in a lower dose (2mg) in combination with ethinyl estradiol (EE), under the brand name of Diane.

Flutamide: It inhibits the androgen receptor and reduces the synthesis of androgens. In clinical practice it is used in doses from 62.5mg to 500mg [65].

According to the Endocrine Society's "Clinical Guidelines for Evaluation and Treatment of Hirsutism in Premenopausal Women 2008" flutamide is not more effective than 100 mg spironolactone and there are some potential side effects, where the most feared side effects are hepatic toxicity and liver failure [66,67]. On the other hand, in a study by Moghetti and coworkers, spironolactone (100mg/day), flutamide (250mg/day), and finasteride (5mg/day) were compared in the treatment of hirsutism among 40 hirsute women. They were randomly assigned to double blind treatments with one of these three drugs or placebo for 6 months. There were no significant changes in safety parameters during the study period. After 6 months of therapy all three groups of women given active drugs showed significant reductions of their hair diameters and a 40% reduction of the Ferriman-Gallwey score. There were no statistically significant differences among groups [68].

Bicalutamide: It is a nonsteroidal pure anti-androgen, indicated for prostate cancer but has been used in half the dose for women with hirsutism due to PCOS [65]. It is however not recommended in Sweden, because of its potential side effects.

Enzyme inhibitors

Finasteride: It inhibits the peripheral conversion of testosterone to Dihydrotestosterone (DHT), by inhibition of type II 5 alpha reductase and is approved for benign prostate hyperplasia. For women with hirsutism it has been used in doses from 1-7.5mg [7,69].

Eflornithine: It was developed for systemic treatment of Human African Trypanosomias (HAT), "West African sleeping sickness". Alopecia turned out to be a common side effect of its systemic administration [70]. As a local preparation it 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 [7,49,69]. One randomized, controlled trial with 594 women found a 26% reduction of hair mass and a 23% reduction in hair length with eflornithine treatment versus vehicle which was statistically significant [71].

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 have been described. When used as directed, percutaneous absorption is minimal. It is proven that topical eflornithine in combination with laser had additive effect of unwanted facial hair and reduced hair regrowth between laser sessions.

A randomized bilateral vehicle-controlled study of eflornithine cream combined with laser treatment versus laser treatment alone for facial hirsutism in women, found a statistically significant better effect in hair removal between eflornithine plus laser compared to laser alone [72]. It can also be used as an adjuvant to pharmacotherapy of hirsutism [73].

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 [16] and a meta-analysis of three trials got the same result (OCP+finasteride or OCP+spironolactone in combination versus OCP alone) [74].

Insulin-lowering drugs

Examples of insulin-lowering drugs are: *Metformin*, *pioglitazone*. Reducing insulin levels pharmacologically attenuates both hyperinsulinemia and thereby hyperandrogenemia, but should only be used in case of concomitant diabetes [50]. The opinion of insulin-lowering drugs in managing hirsutism without hyperinsulinemia has been conflicting. A meta-analysis of 348 candidate studies, with 16 eligible studies suggests that insulin sensitizers provide limited or no important benefit for women with hirsutism. The studies were of low to very low quality. Another weakness was that hirsutism was not the primary outcome measured [75]. 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 [75]. Metformin is commonly used in adolescent girls with PCOS either as first-line monotherapy or in combination with OCPs and anti-androgens. It is used to target hyperandrogenemia, to restore menses, to aid in weight reduction, and to prevent or delay the progression to PCOS in high-risk prepubertal girls [5]. Metformin has been compared with placebo in eight studies. There was no effect on hirsutism in any of the studies [76].

Glucocorticoids: Glucocorticoids, suppress the adrenal glands and thereby the adrenal androgens, but they are restricted to women with hirsutism caused by NCAH [50].

Gonadotrophic-releasing hormone analogs (GnRHa): GnRHA is not recommended for hirsutism as there is insufficient evidence for efficacy in the treatment of hirsutism [13,50,65].

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 waxing is painful and all methods are often associated with some skin irritation and folliculitis. It is however a misunderstanding that shaving leads to more rapid and thicker hair growth. 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% [7]. 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. Hence photo epilation or electrolysis is needed in order to reduce the amount of hair. In treatment of hirsutism with lasers or Intense Pulse Light (IPL), the goals are to destroy the hair follicle and to reduce the hair shaft caliber, without destroying adjacent tissues, a process called selective photothermolysis.

The laser light is transferred into heat when it is absorbed by a chromophore, thus destroying the target by thermal damage. For hair removal melanin is the chromophore. Melanin absorbs light in the red and infrared range of the electromagnetic spectrum (600-1200nm). The pulse width plays an important role in determining selective photothermolysis [77]. The duration of the laser pulse has to be shorter than the thermal relaxation time of the hair follicle in order to minimize collateral thermal damage [10]. The thermal relaxation time is defined as the time it takes for the heated tissue to cool half its peak temperature [78]. The thermal relaxation time of the hair follicle is 40-100 ms for terminal hair follicles measuring 200-300µm [72]. Fluence or energy density (J/cm²) determines the peak temperature within the target structure. Fluence and pulse duration influence the amount of heat absorbed. In order to destroy the hair follicle, both the bulb and the bulge need to be targeted. As the target is melanin, the best result is achieved if the skin is light and the hair is dark, besides there is a greater risk of thermal blisters and hyperpigmentation in individuals with darker skin. Higher fluences have been correlated with greater permanent hair removal, however also with more side effects. Recommended treatment fluences for non-experienced operators are set to a safe level, however not always effective. The clinical endpoint of perifollicular erythema and edema could be a more appropriate method of determining the optimal treatment fluence for the actual patient [79]. To combine Eflornithine cream and laser seem to optimize the treatment result [72].

I. Lasers for hair removal are: Long pulsed Ruby laser (694), Alexandrite (755nm), long-pulsed Nd:YAG (1064nm) and long-pulsed Diode (800-810nm).

Long pulsed ruby lasers (694) was the first device on the market for hair removals and resulted in long term hair reduction

[80]. The long pulsed ruby laser is no longer very much used for hair removal.

II. The long-pulsed alexandrite can be safely used in Fitzpatrick skin phototypes I-III or even IV [81,82]. Long-term efficacy (12 months) for the long-pulsed alexandrite laser ranges from 78% to 85% [83,84].

Finkel et al has reported a 95% hair reduction on sideburns after three to five treatments and a 75% hair reduction on the abdomen [85].

III. Diode laser has been reported to reduce hair count with 22% to 59% [86-90]. High fluence diode lasers with contact cooling have been the state of the art for hair removal. However, that is associated with pain and side effects, especially in patients with dark or tanned skin. Barolet studied high fluence diode laser in a randomised, controlled, bilaterally paired within-patient study. Diode laser therapy with low fluence was well tolerated, safe and efficacious [91]. Recently there are several studies showing comparable hair reduction and fewer side effects with low fluence devices as with high fluence device. The mechanism of hair removal with low fluence diode laser is supposed to be through photomodulation of germinative cells leading to altered hair growth and through induction of hair miniaturization of coarse terminal hair [78].

IPL emits polychromatic non-coherent light with wavelengths from 400-1400nm. For hair removal a filter that filters the wave-lengths below 525-550nm is often used [92]. If an IPL is used for hair removal it should have a dual filter system, i.e. also a water filter that filters wave length above 900nm in order to protect the skin from being burned (Figure 2,3).

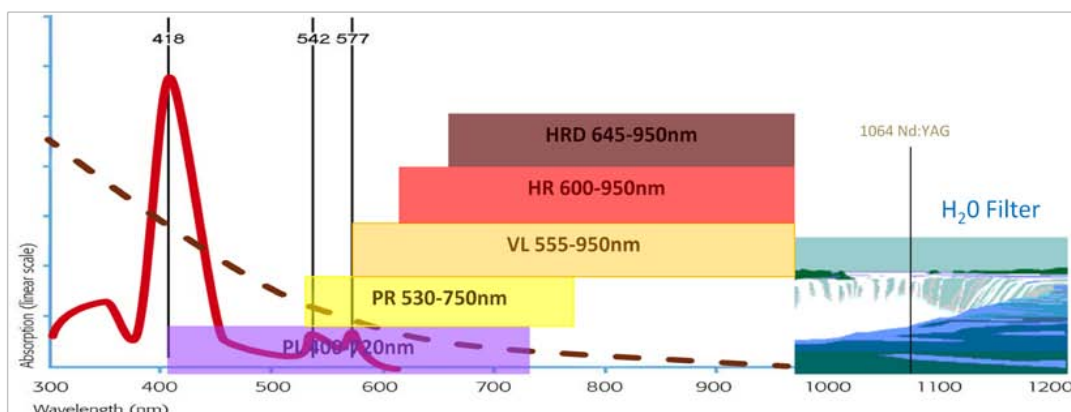
Comparison of Different Devices

Alexandrite and diode are said to be slightly more efficacious in some studies but not to the point of statistical significance [73]. In studies lasers and IPL have been found equally effective [92,93]. A prospective randomized intrapatient, right-left assessor-blinded study compared Nd:YAG vs IPL for hair removal on the leg in 38 patients. The hair follicles were counted before and after each session. There were significant hair reduction after the first session of the Nd:YAG laser treated side. On the IPL treated side the hair reduction became significant after the third treatment. Twelve patients completed the study. Eighteen months after the last treatment session, there were significant hair reduction on both Nd:YAG laser and IPL treated side in 12 patients. The patient satisfaction scores were higher with the IPL because of lower levels of side effects after treatment (pain, edema and burning sensation) [94].

The levels of androgens play an important role for the results of photo epilation. A study in a Dermatological department in Kathmandu in Nepal compared the effect of Nd:YAG laser in relation to the hormonal profile. They found that women with high androgen levels and elevated LH: FSH ratio required more treatment sessions than women with lower levels [95].

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 [79]. After multiple treatments patients can expect approximately a 75% hair reduction [81].

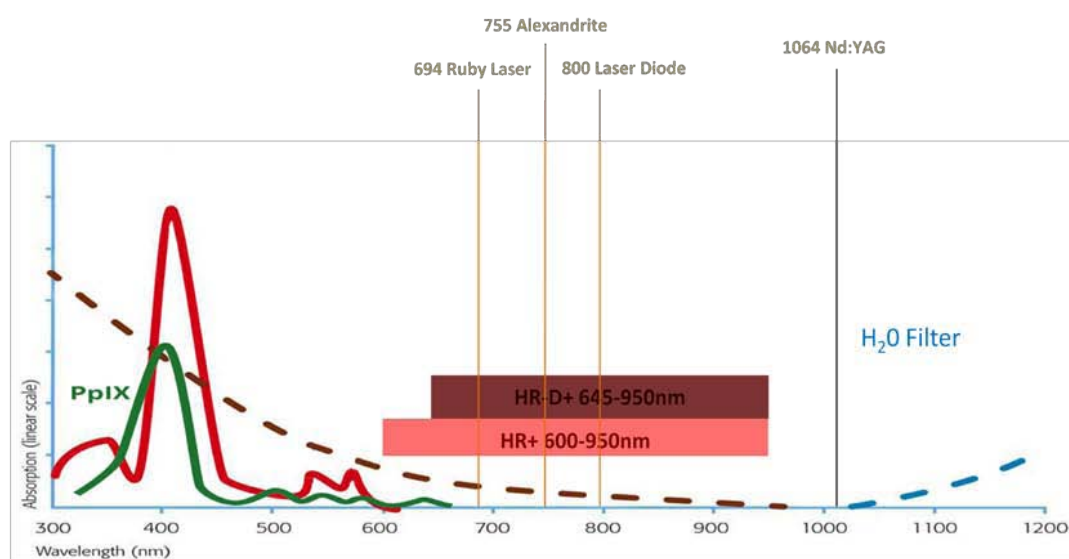
IPL light with dual filters



With curtesy Scanex

Figure 2 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.

Wavelengths in hair removal lasers and IPL



HR+ Hair removal
HR-D+ Hair removal dark skin
With curtesy Scanex

Figure 3 + Absorption

- Penetration
- Absorption
- + Penetration

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.

Home-Use devices: There are several devices on the market for example diode laser and IPLs. The effectiveness in the long term need to be further studied. There are however several studies demonstrating hair reduction from 10% to even 72% after three to six months follow-up [78].

Patient care

Education of the patient: It is important to give the patient realistic expectations and to inform the patient so unnecessary side effects could be avoided. The patient should be informed that about 80% respond to hair laser therapy after several sessions [96]. Sun avoidance should be emphasized, as there is a higher risk of epidermal damage in sun-tanned skin [81]. Perifollicular erythema and edema is what most patients have to expect after laser therapy. Potential side effects are pigmentary alterations, scarring, blistering, crusting, erosions purpura and folliculitis [97]. Patients should be informed of the risk of reactivation of herpes simplex virus. Valaciclovir 500mg-1g orally twice daily for 7 to 10 days have been recommended [98,99]. To start the day prior to facial laser surgery is advisable [98].

Pretreatment care: Before laser or IPL treatment, the skin should be cleaned and all makeup should be removed [100]. The hair should be shaved so that the light can be absorbed in the hair follicle to allow the thermal damage to occur in the follicle and not on the skin surface [81]. Most women don't consider the photo epilation painful enough to require anesthesia. Mostly the devices have some kind of cooling (either contact or delayed cooling devices) to alleviate pain and discomfort and to prevent unwanted hyperpigmentation or burns. Topical anesthetic creams could be used on sensitive areas, but with great care, as there is a risk of giving too high fluences without the patient protesting. Eye shield must be used both on the patient and the operator during laser- or IPL-treatment.

Post laser care: After therapy patients should be given ice package and a corticosteroid cream to reduce swelling and to decrease pain. Patient should be informed of the importance of avoiding sun exposure for at least 8 to 12 weeks.

NON PHARMACOLOGICAL TREATMENT OF HIRSUTISM RELATED TO PCOS

Weight reduction

Even if weight reduction is difficult to achieve its importance must be stressed to obese women with hirsutism. It decreases serum-insulin, ovarian androgen production and the conversion of androstendione to testosterone and increases sex hormone-binding globulin production [101]. It reduces the cardiovascular risk and could prevent diabetes. Referral to a dietician may be needed to get a "diet plan" and a plan for physical exercise should also be included in the strategy for weight reduction. A prescription for exercise could be an effective way of helping the patient. However it is not proven that weight reduction leads to a reduction of hair in women with hirsutism [102].

CONCLUSION

- Hirsutism is mostly a symptom of underlying androgen excess. It causes profound stress in women and has a negative impact on their quality of life.

- Treatments may need to incorporate pharmacological therapies, cosmetic procedures, and psychological support and a multidisciplinary collaboration.
- To give the patient a diagnosis and information about hirsutism is crucial.
- Basal laboratory tests before treatment is advisable (s-testosterone, SHBG, DHEAS, FSH, LH, s-prolactin, TSH). Further investigations could be needed.
- An ultrasound of the ovaries should be performed, 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 Eflornithine if tolerated.
- Spironolactone is the first choice if an antiandrogen should be used.
- Antiandrogens should be combined with OCP.
- Treatment should not give serious side effects as hirsutism per se is a benign disease.

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