Hirsutism – medical and cosmetic point of view

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Abstract

Hirsutism is a serious clinical and cosmetic problem. According to different studies it affects from 3% to 10% of women in the Polish population. The underlying causes very often include hormonal disorders among which the most common cause is polycystic ovary syndrome (PCOS). Other causes include congenital adrenal hyperplasia, hyperprolactinemia, ovarian and adrenal tumors secreting androgens, Cushing’s syndrome, acromegaly or obesity, use of pharmaceuticals increasing the level of androgens and/or prolactin. Treatment of hirsutism apart from cosmetic procedures is related to the hormonal therapy. Selection for such therapy should depend on the results of a thorough and competent endocrinological evaluation.

Key words: hirsutism, polycystic ovary syndrome (PCOS), acne, testosterone

Introduction

Hirsutism is the term that we use for excessive male type hair observed in women and developed as a result of increased effect of androgens and/or increased sensitivity of skin to their effect. As a symptom of hyperandrogenism hirsutism is often observed together with other symptoms of masculinisation such as: acne, male type hair loss (baldness), seborrhea, macroclitoris, lowering of the voice timbre and defeminization including anovulation, menstrual disorders. The increase of androgens secretion that often underlies hirsutism is also related to of metabolic changes such as hyperinsulinemia, insulin resistance, obesity, alterations in the lipid profile. The frequency of hirsutism symptoms varies depending on geographical location. In Poland, according to different authors the problem affects from 3 to 10% of women in the general population. Asian women have usually less hair on their bodies than women from the Mediterranean Sea region. The frequency of these symptoms varies also with age: hair above the upper lip is observed in around 30% of women after menopause [1, 2].

Mental aspects of hirsutism

Physical appearance, especially for women, plays an important role. Women try to adjust their physical appearance to common standards, however there is a huge gap between the beauty canons promoted nowadays and the realistic appearance of most of the people. Skin conditions in the form of hirsutism, acne or hair loss arising from a disease may significantly interfere with psychological and social functioning of a patient [3].

Physical appearance and perception thereof is inseparable from self-assessment, self-esteem and self-confidence. Problems with acceptance of one’s physical appearance may lead to mental disorders and become the cause of depressive mood. Physical appearance may to a large extent affect one’s adaptation in society. Skin conditions may significantly deteriorate the quality of life leading to shame and embarrassment and negatively affecting one’s self-assessment causing withdrawal and isolation [4].

Psychodermatology is a relatively new discipline of medicine which describes the interactions between skin conditions and psychiatry and psychology. Among the most common mental disorders in the group of patients suffering from skin conditions the following are identified: mood disorders (particularly depression type), suicidal thoughts and tendencies, anxiety, obsessive and paranoid disorders. Psychodermatological conditions include disorders with both psychological and dermatological components present. Hirsutism is one of such conditions [5].

Etiology of hirsutism

The occurrence of the symptoms of hirsutism and other symptoms of hyperandrogenisation is caused by intensified production of androgens within the ovaries and/or adrenal glands, decreased sex hormone binding globulin (SHBG) binding of androgens, decreased synthesis of SHBG, increased conversion of weak androgens such as dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS) into stronger ones such as: androstendione or testosterone. Genetically conditioned sensitivity of target organs to appropriate or increased level of androgens plays a crucial role [6].

The most common cause of hirsutism in women is polycystic ovary syndrome (PCOS). Hirsutism is observed in around 90% of the diagnosed patients. It is related mainly to the increase of serum androgens (testosterone, androstendione, DHEA) and the decrease of serum SHBG.
concentration. Hyperthecosis is a manifestation of PCOS which is characterized by particularly intensive hirsutism and common co-occurrence of other symptoms and metabolic consequences of hyperandrogenisation. In this clinical case, intensified processes of fibrosis are observed in the region of the ovaries with clearly visible overgrowth of the stroma (connective tissue) and acanthosis nigricans (weakened hyperpigmented skin with keratosis found in the area of neck, axilla and groin) resulting from intensified metabolic alterations of insulin resistance type or hyperinsulinemia [7]. The basis for diagnosing PCOS is the clinical picture where, apart from hyperandrogenisation symptoms, the following are often observed: obesity, menstrual disorders and anovulation. Increased serum concentration of testosterone and androstendione in blood is found as well as increased concentration of LH and increase in the relation of LH/FSH, elevated concentration of insulin and decreased concentration of estradiol and SHBG are observed. Ultrasound examination test is very important in the diagnosis as it shows the characteristic image of the ovaries. The ovaries are enlarged with a thickened tunica albuginea, overgrown recess and small follicles located at the circumference. Anovulation observed in these patients is related to a gonad structure that is stable in the course of time (ovulation is found only in around 10% of women suffering from PCOS). Final diagnosis should constitute a synthesis of the mentioned symptoms and additional tests results and it should be made by a specialist who deals with the problems of gynecological endocrinology [7, 8].

Another relatively common cause of hirsutism is congenital adrenal hyperplasia (CAH) where against the background of enzyme blocks (deficiency of 21-hydroxylase, 11-hydroxylase, 17-hydroxylase, 3-beta-ol dehydrogenase and 20-22 desmolase) the adrenal secretion of androgens (mainly androstendione) and cortisol precursors increases. In patients with this diagnosis elevated concentration of 17-0H progesterone is observed (4-6 times higher than the standard) and the increase of the level of this hormone after administration of ACTH. It is often found that also the concentration of testosterone, androstendione, DHEAS is elevated. The concentration of LH, FSH, cortisol and ACTH are usually within the standard limits [9].

An important and relatively common cause of hirsutism is hyperprolactinemia. The increase in prolactin secretion leads to intensified stimulation of adrenocortical glands by ACTH and elevated concentration of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone (DHEA-S). As a result of decreased estrogens concentration in hyperprolactinemia the decrease in SHBG concentration is observed and therefore also the increase of free fractions of androgens. The total amount of testosterone remains unchanged. Due to the fact that the elevated concentration regards androgens that have little activity, the symptoms in a form of hirsutism are in this case not intensive [10].

Among the causes of hirsutism also ovarian and adrenal tumors secreting androgens are reported. The most common are: Sertoli-Leydig cell tumor, thecoma, hilar cell tumor, sometimes granulosa theca cell tumors. Hirsutism may be also caused by a tumor of gonadoblastoma type as well as the production of excessive amount of androgens as a consequence of proliferation of the stroma cells of hormonally inactive ovarian tumors such as Krukenberg tumor, pseudomucinous cystadenoma, Brenner tumor or epithelial adenocarcinoma [11].

Other causes of hirsutism include Cushing syndrome, acromegaly or obesity.

Abnormal hair occurrence may be also related to administration of pharmaceuticals that are characterized by androgen activity or may lead to hirsutism associated with hyperprolactinemia. The following may be mentioned here: anabolic steroids, progestagenes with androgens activity, danazol, antihypertonic, anticonvulsants, streptomycin, histamine receptor blockers administered in the treatment of gastric and duodenal ulcer. The occurrence of iatrogenic hirsutism should be treated as a basis for reconsideration of recommendations made with regard to the therapy and potential change of the administered medicine [12].

Idiopathic hirsutism can be defined as excess terminal hair production in a male-like pattern in androgen-receptive body parts of patients who show no signs of endocrine or androgen disorders. This kind of hirsutism occurs in the presence of regular ovulation and normal androgen levels. Some of the patients from this group were diagnosed with intensified activity of 5α-reductase – the enzyme that is responsible for transformation of testosterone and androstendione in their more active form of dihydrotestosterone in hair follicles. Another process that takes place within the skin is the transformation of dihydrotestosterone into alfa-androstendioni under the influence of 3-alfa and 3-beta reductases with participation of 17 beta-hydroxysteroid dehydrogenase. The biological role of these metabolites remains unknown. The research conducted in recent years indicate that they participate in androgenisation of the system particularly in the area of sebaceous glands and hair follicles. Differences in the conversion of testosterone are also observed in dihydrotestosterone depending on the area of the skin. Increased metabolism of androgens has been stated in the area of skin that is affected with acne vulgaris. Clinical practice requires to separate this group especially when this abnormality is found in family history [13].

Therapy of hirsutism

Regarding hirsutism treatment, the most common cosmetic procedures include the application of skin
whitening creams, depilation, laser and hormonal drugs. Unfortunately, all these treatments, have a short-lived effect. All treatments should be regarded as a complement to pharmacological treatment.

The treatment of hirsutism is particularly justified in cases when the underlying factor is the elevated level of serum androgens which may lead to disorders of the menstrual cycle, anovulation and metabolic changes of insulin resistance, hyperinsulinemia and hyperlipidemia type. Additional justification to start treatment is the increased frequency of infertility observed in these women as well as obesity, diabetes type 2, ischaemic heart disease, endometrium cancer. The treatment of hirsutism aims at: decreasing the secretion of androgens (ovaries, adrenal glands, peripheral tissue), increasing SHBG level in the serum and blocking the receptors for androgens in peripheral tissue.

The most common group of medicines administered in the treatment of hirsutism are anti-androgens among which special attention should be drawn to cyproterone acetate. Cyproterone acetate is a derivative of 17-hydroxyprogesterone with anti-androgenic and anti-gonadotropic effect. The anti-androgenic effect of the drug is primarily related to the decreased effect of 5a-reductase in the skin and blocking the competence of dihydrotestosterone binding with the receptors in peripheral tissue. Cyproterone acetate decreases the biosynthesis of androgens by hindering the effect of 17-hydroxylase and 17,20-desmolase enzymes, increasing at the same time the metabolic clearance of testosterone by intensifying the activity of liver enzymes. The anti-gonadotropic effect is connected with strong inhibition of lutropin secretion which indirectly causes decrease of ovarian androgens synthesis. Additionally, cyproterone acetate also shows a weak glucocorticosteroid effect decreasing the secretion of adrenocorticotropic hormone (ACTH) [14].

Cyproterone acetate is administered in a daily dose from 25 to 100 mg in the first phase of the cycle (since 5th to 14th day of the cycle) together with oral estrogenic-progesteronic preparations. Indications for this type of treatment include intensified hirsutism, androgenic dependent hair loss, severe cases of acne and/or seborrhoea. Clinical results of the therapy are to be seen after around 3 months; decreased intensity of acne, hirsutism and skin conditions connected with subhorrea is observed. Clinical improvement regarding acne and subhorrea is observed in 90% of cases during 3-6 months of treatment. The resolution of acne has been observed to appear a little earlier i.e. already after 2 months of treatment, resolution of hirsutism took longer. Androgenic hair loss is decreased in 40% of cases, whereas improvement is achieved only after at least 9 months of treatment. In parallel decreased concentrations of androstendione, testosterone and lutropin are found in the blood serum. After ceasing the treatment the androgenic effect is maintained for around 3 months, therefore some authors recommend 3-months long break after half a year of drug administration. Prolonged effect is a consequence of storing the drug within the fat tissue which may result in delayed drug-withdrawal bleedings in obese women. Among the side effects of the treatment the most commonly reported are: body weight gain (up to 45% of patients), nausea and vomiting (25%), breakthrough bleeding (20%) and decrease of libido (10%). Large doses of cyproterone acetate cause additional symptoms dependent on the excess of gestagens such as: physical weakening (42%) and decreased vitality (14%). In tests carried out on animals teratogenic effect of cyproterone acetate was stated and that is the reason why the drug cannot be used during pregnancy and should always be accompanied by contraceptives. Another reason why the drug should be used together with estrogens is the fall of HDL level observed during the time of treatment, which may be connected with the increase of atherosclerosis risk. This effect is not observed when estrogens are administered in parallel. Cyproterone acetate is secreted with milk in 0.2% [15].

Cyproterone acetate in a dose of 2 mg in combination with ethynylestradiol is recommended in case of less intensified hyperandrogenisation syndromes such as: acne in women who wish to use contraceptives simultaneously (also in case of acne with coexisting subhorrea and inflammatory lesions in the area of hair follicles) and in case of benign forms of hirsutism and androgen-dependent hair loss.

Cyproterone acetate in a dose of 1 mg in combination with estradiol valerate is recommended in women for whom the administration of synthetic estrogens increases the risk of thrombosis and in women in perimenopause age. Lower dose of cyproterone acetate in the therapy correlates with smaller improvement in hyperandrogenisation symptoms.

Other drugs with anti-androgenic effect include spironolactone. Spironolactone inhibits dihydrotestosterone (DHT) binding with receptors and blocks the activity of 5 alpha-reductase in the skin and the activity of 17-beta-hydroxylase and 17, 20-desmolase in adrenal glands. Spiro- nolactone is a drug of choice in case of hirsutism co-existing with obesity and arterial hypertension. It is used in monotherapy in a dose of 100-200 mg/day or in combination with contraceptives in a dose of 100 mg/day. The following side effects are reported among: irregular menstruations, excessive urination, tiredness, nausea, headaches and decrease of libido, hypocalemia and hypotonia are rare.

Flutamid is another androgen used in the treatment of hirsutism. This preparation is not available in Poland. It is a non-steroid drug. The mechanism of its activity consist of strong inhibition of the activity of 5a-reductase. In comparison to the drugs mentioned above it
does not demonstrate estrogen, progestagenic, corticosteroid and antigonadotropin effect. The use of this drug is very limited due to serious but rare complication such as hepatitis. Therefore it is recommended that during the treatment liver functions tests are performed and monitored and that the therapy be interrupted immediately when nausea, vomiting or hepatitis is observed. During the time when the drug is administered it is also recommended that effective contraception be used due to its teratogenic effect. Another know side effects of the drug: dry skin (60% of patients), increased appetite (30%) and the fall of libido (5%).

Finasteride is another medicine used in the treatment of hirsutism. Drug effect’s mechanism in the treatment of hirsutism consists in blocking 5-alfareductase in the skin. In the treatment of hirsutism the drug is used in a dose of 5 mg/day. However there are reports about similar effectiveness of smaller doses. The effectiveness of the drug in the treatment of hirsutism is comparable with the effectiveness of spironolactone in a dose of 100 mg/day. The clinical effect is visible already after 3 months of administration. The advantage that does not raise any doubts is the fact that the drug has no side effects. When recommending the drug one should remember about effective contraception (hermaphroditic genitalia in male fetuses).

As it was mentioned when discussing cyproterone acetate an important role in hirsutism treatment is played by administration of estrogenic and gestagenic preparations in sequential or cyclical therapy. This kind of treatment inhibits the secretion of LH, increases the synthesis of SHBG, lowers the concentration of free T and activity of 5α-reductase. In this type of proceeding estrogenic and gestagenic preparations intended for hormonal therapy are used as well as contraceptive pills with two components.

Hyperandrogenisation of ovarian origin it is also recommended to apply gonadoliberin analogues. Administration thereof causes inhibition of gonadotropin secretion and as a consequence inhibition of steroidogenesis in the ovary decreasing the production of androgens. However, hypoestrogenism related to the administration of GnRH analogues leads to the occurrence of numerous side effects, among others: neurovegetative and atrophic symptoms resembling the ones observed during menopause, therefore it is necessary to additionally use low doses of steroid hormones. In the long run this kind of treatment leads to decrease of bones density and osteoporosis.

Hyperinsulinemia and insulin resistance that often coexist with hirsutism require additional procedure in order to increase the target tissue’s sensitivity to insulin. The easiest way is non-pharmacological procedure leading to body weight loss (diet low in calories, physical activity). If this does not bring any effects, it is necessary to additionally apply metformin (3 × 500 mg daily during 8 weeks). A modern preparation that improves cells’ sensitivity is troglitazone. This preparation has a positive effect on ovarian steroidogenesis and LH secretion by reducing the concentrations of insulin [16].

In case of PCOS, the intensifying hirsutism, lack of improvement after conservative treatment or side effects of hormonal therapy constitute indications for taking the decision about surgical treatment using laparoscopy. Surgical treatment should be considered especially in case of hyperthecosis. Positive effects of the surgery in the form of regular menstrual cycles are observed in 85-90% women. The possible ground for the effectiveness of contemporary surgical treatment is the elimination of mechanical obstacle to ovulation through removal of thickened bag and the reduction of the stroma tissue that generates androgens and the number of atretic follicles producing estrogens. What is also significant is that the improved blood supply of the ovary which has been reduced in the surgery [17].

Surgical treatment is recommended also in the treatment of hormonally active tumors of an ovary. The treatment is based on the removal of the tumor and if the tumor is big or malignant features are observed, it is necessary to remove the uterus together with appendages. If there are no features of malignancy in the tumor, the prognosis is good and hirsutism resolves in several months after the surgery [18].

Treatment of hyperandrogenisation related to adrenal glands may be referred glikocorticosteroids use. They inhibit the secretion of ACTH, compete with DHT in the receptors, inhibit the activity of aromatase system. The most commonly used are: dexamethasone, hydrocortisone and cortisol.

The symptoms of hirsutism in the course of hyperprolactinemia are mitigated as a result of administering derivatives of bromocriptine, quinagolide or cabergoline [19].

Patients suffering from Cushing syndrome or disease should be operated on – the removal of pituitary or adenocortical adenoma, pituitary radiotherapy is also applied.

To sum up one should emphasize the necessity to perform a detailed endocrinological evaluation basing on thorough clinical and hormonal diagnostics in cases when intensified hirsutism is found or when hirsutism coexist with other symptoms of hyperandrogenisation. As far as the effectiveness of treatment is concerned none of the mentioned drugs allows absolute curing. Suppression of the progress of abnormal hair growth during treatment is maintained for 3-6 months after ceasing the treatment and after this time hair growth is observed again.

References

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