Outlook

Medical treatment regimens of hirsutism

Yilmaz Sahin obtained his MD degree in the School of Medicine, Ankara University, Ankara, Turkey. He completed his residency at Dr Zekai Tahir Burak Women's Hospital, Ankara in 1983. He is currently a Professor of Obstetrics and Gynecology at the University of Erciyes, Kayseri, Turkey. His interests include reproductive endocrinology, polycystic ovary syndrome, hirsutism and endoscopic pelvic surgery.

Dr Yilmaz Sahin

Fahrettin Kelestimur received his MD degree in 1979 from the School of Medicine in the University of Hacettepe, Ankara, Turkey. After completing his residency in 1984 in the School of Medicine at the University of Erciyes, Kayseri, Turkey, he trained in endocrinology at St Bartholomew's Hospital, London, UK. This was completed in 1992 and he became a professor in 1995. He is currently consultant in the Department of Endocrinology of Erciyes University, School of Medicine. He is executive committee member of the European Neuroendocrine Assocation. His interests are neuroendocrinology, reproductive endocrinology and pituitary medicine.

Dr Fahrettin Kelestimur

Yilmaz Sahin[1,3], Fahrettin Kelestimur[2]
[1]Department of Obstetrics and Gynecology, Erciyes University, Medical School, 38039, Kayseri, Turkey
[2]Department of Endocrinology, Erciyes University, Medical School, 38039, Kayseri, Turkey
[3]Correspondence: e-mail: ysahin@erciyes.edu.tr

Abstract

Hirsutism, which is a common clinical problem in women of reproductive age, is characterized by excessive growth of terminal hair in the androgen-sensitive skin regions. It is the result of either androgen excess or increased sensitivity of the hair follicles to normal levels of androgens. The management, which includes cosmetic measures and medical treatment, is far from satisfactory. Anti-androgen drugs play a key role in the treatment of hirsutism, but they have some side-effects which may result in cessation of the drug. On the other hand, anti-androgen treatment often needs to be continued for a long time. So, safe, inexpensive, and effective anti-androgen drugs are needed. Recently low-dose anti-androgen drugs have been shown to be effective in the maintenance of treatment. On the other hand, cyproterone acetate plus ethyniloestradiol and spironolactone, cyproterone acetate plus ethyniloestradiol and finasteride, and spironolactone and finasteride combinations have been used succesfully in decreasing the hirsutism score. There are also some promising data regarding the effects of insulin sensitizers in the treatment of hirsutism, particularly in patients with polycystic ovarian syndrome. In the present review, the main features of anti-androgen drugs, new combined treatments, and insulin sensitizers in the treatment of hirsutism are discussed.

Keywords: *cyproterone acetate, finasteride, flutamide, hirsutism, metformin, spironolactone*

Introduction

Hirsutism is characterized by excessive growth of terminal hair in the androgen-sensitive skin regions in women and affects 5–8% of the whole female population of fertile age (Falsetti *et al*., 1998). Hirsutism is the result of either androgen excess or increased sensitivity of hair follicles to normal levels of androgens. Some drugs, polycystic ovarian syndrome (PCOS), non-classic congenital adrenal hyperplasia (NCAH), Cushing's syndrome, acromegaly and ovarian and adrenal tumours may be the underlying causes or hirsutism may be idiopathic (Ünal *et al*., 1993; Kelestimur *et al*., 1996; Conn and Jacobs, 1997;

Sahin and Kelestimur, 1997; Kelestimur, 2001a). PCOS and idiopathy are the most common causes of hirsutism.

Before treatment for hirsutism is started, a careful medical history, particularly relating to drugs that may cause excess hair, and clinical examination are necessary to identify the underlying cause. A differential diagnosis must be made between hirsutism and hypertricosis which is characterized by increased vellus hair. The underlying cause should be identified and corrected where possible, but sources of androgen excess in patients with hyperandrogenism and hirsutism can rarely be permanently removed. For this reason, treatment is long-term and either continuous or intermittent. In addition, a very long treatment period may be required to prevent the reappearance of hirsutism. However, not enough information is available regarding maintenance treatment of hirsutism. Recently, low-dose anti-androgen drugs have been suggested for maintenance treatment. Any anti-androgen drug should be inexpensive, clinically effective, safe and suitable for long-term use. Unfortunately there is no ideal drug that has all these features. However, there have been major developments in the treatment of hirsutism in recent years.

The combination of an anti-androgen with an oral contraceptive drug, which is a well-known option in the treatment of hirsutism, is outside the scope of this review. After giving brief information about the drugs available for the treatment of hirsutism, the review discusses recent developments including the introduction of insulin sensitizers and different combinations of anti-androgen drugs in the treatment of hirsutism.

Medical treatment of hirsutism

Anti-androgen drugs are a cornerstone in the medical treatment of hirsutism. Some recent data suggest that insulin sensitizers may also be beneficial in decreasing hirsutism score. Hirsutism is scored using systems revised by Thomas and Ferriman (1957) and Ferriman and Gallwey (1961). **Table 1** shows the main anti-androgen drugs, their new combinations, and insulin sensitizers used in the treatment of hirsutism.

Anti-androgen drugs

Spironolactone

Spironolactone is one of the anti-androgen drugs that is most commonly used effectively for long periods in the treatment of hirsutism. Spironolactone is an aldosterone antagonist that competes with androgens for the androgen receptor and inhibits the interaction of dihydrotestosterone (DHT) with its intracellular androgen receptor. Spironolactone increases the metabolic clearance of testosterone and inhibits androgen production by inhibiting cytochrome P450, particularly at high doses (Lobo *et al*., 1985; McMullen and Van Herle, 1993). In a recent study, it has been reported that spironolactone therapy might result in significantly increased sex-hormone binding globulin (SHBG) levels at the end of a treatment period of one year (Kelestimur *et al*., 2004).

Spironolactone is given in the treatment of hirsutism in doses ranging from 25 to 400 mg daily and the effect is dose-related. (McMullen and Van Herle, 1993; Rittmaster, 1999). Larger doses are more effective but result in more side-effects. The authors recommend 100 mg daily, which is a clinically effective and safe dose. Erenus *et al*. (1997) compared the efficacy of spironolactone (100 mg daily) and finasteride (5 mg daily) in idiopathic hirsutism, and they found that there was a significantly better response with spironolactone treatment at the end of 9 months. In a recent study, the efficacies of spironolactone (100 mg/day), flutamide (250 mg/day), and finasteride (5 mg/day) were compared, and after a 6-month course of therapy, the clinical efficacies of these drugs were found to be similar, but spironolactone was the most cost-effective drug (Moghetti *et al*., 2000a). The effectiveness of cyproterone acetate (CPA), finasteride and spironolactone has been compared in a prospective randomized clinical study in patients with idiopathic hirsutism. At 6 months of therapy, the reduction of hirsutism was similar in patients who used CPA, finasteride or spironolactone. However, 1 year after therapy, spironolactone was found to be significantly more effective (Lumachi and Rondinone, 2003). In an extensive analysis including all publications of randomized controlled trials of spironolactone versus placebo and/or in combination with steroids (oral contraceptive pill included), it was concluded that six months' treatment with 100 mg daily spironolactone compared with placebo was associated with a statistically significant subjective reduction in hair growth and a decrease in Ferriman–Galwey scores (Farquhar *et al*., 2001).

The side-effects of spironolactone include hyperkalaemia, transient polyuria, gastrointestinal discomfort, nausea, breast tenderness, allergic reactions, somnolence, headache, vertigo and menstrual irregularity. Most of these side-effects are generally not a problem and are rarely the cause of the cessation of treatment. The most common side-effect of spironolactone is polymenorrhoea which has been reported in 50 to 60% of the patients (Moghetti *et al*., 2000a; Kelestimur *et al*., 2004). Irregular menstrual bleeding can be managed by addition of an oral contraceptive.

Table 1. Anti-androgen drugs, their new combinations, and insulin sensitizers used in the treatment of hirsutism.

Anti-androgen drugs and the new combinations
Anti-androgen drugs
Spironolactone
Cyproterone acetate
Finasteride
Flutamide
Anti-androgen combinations
Cyproterone acetate and ethinyloestradiol plus spironolactone
Cyproterone acetate and ethinyloestradiol plus finasteride
Cyproterone acetate and ethinyloestradiol plus flutamide
Spironolactone plus finasteride
Insulin sensitizers
Metformin
Thiazolidinediones

Spironolactone can be used safely, it has no major side-effects, it is clinically effective for a long time and is relatively inexpensive.

Cyproterone acetate

CPA is a powerful progestogen that also acts as an anti-androgen at target sites. It is derived from 17α-hydroxyprogesterone. CPA inhibits the action of testosterone and dihydrotestosterone by binding to intracellular receptors, and decreases ovarian testosterone secretion by inhibiting LH release (Conn and Jacobs, 1997). CPA may also reduce adrenocorticotrophic hormone (ACTH) secretion, and for this reason it is beneficial in both adrenal and ovarian hyperandrogenism (Girard *et al*., 1978). It has been reported that CPA might also inhibit 5α-reductase activity (Fruzzetti *et al*., 1999).

There are two forms of CPA: a 50 mg tablet and Diane 35 (2 mg CPA and 35 μg ethinyloestradiol). It may be used as 50 mg CPA daily during the first 10 days of the cycle. CPA is generally used in combination with oral ethinyloestradiol. The beneficial effect of CPA plus ethinyloestradiol seems to be related to the decrease in plasma levels of total and free testosterone, androstenedione, dihydrotestosterone and to the increase in SHBG concentrations (Rubens *et al*., 1984). Barth *et al*. (1991) found that either 20 mg or 100 mg CPA produced a faster initial response than 2 mg, but no difference was noted at 12 months. Pazos *et al*. (1999) compared triptorelin, CPA and flutamide in 39 hirsute women. They have found that flutamide was more effective than CPA but CPA was found to be satisfactorily effective at a much lower cost.

The side-effects of CPA include weight gain, oedema, decreased libido, headache, hepatotoxicity, fatigue, enlargement of mammary glands and mood changes. On the other hand, an increased risk of venous thromboembolism due to CPA plus ethyniloestradiol was reported recently in women with hirsutism (Seaman *et al*., 2003). Shortness of breath was reported as a rare side-effect due to high dose, 50 mg/day, CPA (Mallari and Sinclair, 2002). It is one of the most commonly used therapeutic agents worldwide for hyperandrogenism, PCOS and idiopathic hirsutism.

CPA is an effective and relatively safe drug when it used at a low dose but hepatotoxicity should be kept in mind.

Finasteride

Finasteride blocks the conversion of testosterone to the more potent DHT by 5α-reductase. It binds to this enzyme and interferes with its action. It does not bind to the androgen receptor and has no effect on testosterone secretion. The fall in serum DHT is accompanied by a reduction in metabolites of DHT such as 3α-diol glucuronide and a rise in plasma testosterone concentrations. Finasteride is more effective against isoenzyme 5α-reductase type 2 (found in genital skin and the prostate in the male) than type 1 (non-genital, scalp) but the specificity towards the two isoenzymes is incomplete (Dallob *et al*., 1994; Rittmaster, 1995).

Numerous studies have demonstrated that finasteride is an effective drug in the treatment of hirsutism (Moghetti *et al*., 1994; Castello *et al*., 1996; Erenus *et al*., 1997). It has previously been shown that finasteride decreases hirsutism score significantly without any side-effects (Sahin *et al*., 1998; Bayram *et al*., 1999). At present, 5 mg is recommended as the daily dose in women; no added effectiveness has been demonstrated at higher doses (Conn and Jacobs, 1997). An oral 5 mg dose of finasteride was administered for 3 months to 10 hirsute women to determine the effect on gonadotrophin secretion; finasteride significantly decreased hair growth without negatively affecting gonadotrophin secretion (Fruzzetti *et al*., 1994). Wong *et al*. (1995) studied 14 women with moderate to severe hirsutism and concluded that despite significantly different effects on androgen levels, finasteride and spironolactone treatment had similar clinical effects on hirsutism.

Fruzzetti *et al*. (1999) compared the clinical and endocrinological effects of CPA, flutamide, and finasteride in 45 hirsute women and found that finasteride, CPA, and flutamide are equally effective in decreasing hirsutism. Despite the change in total testosterone levels, a slight but non-significant increase in free testosterone was observed during the last 6 months of therapy, with no significant change in plasma SHBG concentrations after finasteride treatment. In another study, the effects of finasteride were compared with flutamide in the treatment of hirsutism in 64 patients with PCOS and 46 with idiopathic hirsutism and it was found that finasteride reduced the Ferriman–Gallwey score by 31.4% in the patients with PCOS and by 34.2% in the patients with idiopathic hirsutism, and hair diameter by 27.0–34.1% in PCOS and by 29.6–37.9% in idiopathic hirsutism. Finasteride increased testosterone levels by 40% in PCOS and by 60% in idiopathic hirsutism and decreased 3α-diole glucuronide (Falsetti *et al*. 1999).

A significant decrease in hirsutism score has been demonstrated in 35 women after 12 months of treatment with a standard dose of finasteride (5 mg/day) (Bayram *et al*., 1999). In a prospective study including 29 hirsute women, low-dose (2.5 mg/day) finasteride decreased the hirsutism score from a mean of 18.4 ± 4.6 to 8.4 ± 4.2 after one year of treatment. The percentage reduction in hirsutism score at 6 and 12 months was 29.2 ± 14.5 and 55.7 ± 14.9%, respectively. (Bayram *et al*., 2003).

The authors have recently compared the long-term clinical and hormonal effects of a standard dose (5 mg/day) of finasteride with a lower dose (2.5 mg/day) in hirsute patients. Low-dose (2.5 mg/day) finasteride had a similar effect to high-dose finasteride (5 mg/day) and it is suggested that low-dose (2.5 mg/day) finasteride may be used instead of high-dose (5 mg/day) because of its reduced cost. Both low- and high-dose finasteride did not change FSH, LH, testosterone, androstenedione, SHBG, 17-hydroxyprogesterone or dehydroepiandrosterone sulphate (DHEA-S) levels. (Bayram *et al*., 2002).

Finasteride is a safe, moderately effective but expensive drug in the treatment of hirsutism.

Flutamide

Flutamide is a non-steroidal compound that seems to act only at the androgen receptor site and is therefore considered a 'pure' peripheral androgen antagonist. It does not have a progestogenic or antigonadotrophic action. It does not cause menstrual irregularity.

In a prospective randomized study, flutamide (250 mg twice a day) was found to be similarly effective to spironolactone (100 mg daily) in idiopathic hirsutism (Erenus *et al*., 1994). Falsetti *et al*. (1999) compared the effectiveness of flutamide and finasteride in the treatment of hirsutism in patients with PCOS and with idiopathic hirsutism. The patients were assigned randomly to receive 5 mg finasteride once daily or 250 mg of flutamide twice daily, for 12 consecutive months. Flutamide was found to be significantly more effective than finasteride in the treatment of hirsutism. It did not modify the hormone profile in women with PCOS or idiopathic hirsutism. Two (3.6%) patients receiving flutamide expressed abnormal transaminase levels after 6 months of treatment. Flutamide induced dry skin in 67.3% of cases. In another study, 5 mg finasteride once daily or 250 mg of flutamide twice daily were compared in patients with idiopathic hirsutism, and flutamide was found to be more effective than finasteride (Falsetti and Gambera, 1999).

Cesur *et al*. (1994) treated 19 women with flutamide, 500 mg/day for one year, and found a significant decrease in hirsutism score. Marugo *et al*. (1994) evaluated the clinical efficacy of flutamide on the course of hirsutism. They found a marked clinical improvement in the degree of hirsutism in all patients. Testosterone and free testosterone fell significantly in both groups, while SHBG concentrations showed an increase in PCOS. During flutamide treatment, androstenedione levels were slighly but significantly decreased in the patients with PCOS. Basal plasma DHEA-S levels were significantly suppressed by flutamide only in PCOS women. They concluded that although the main action of flutamide can be attributed to its peripheral anti-androgenic properties, the decrease in circulating androgen observed during treatment suggests that it can also modulate androgen production and/or metabolism. The safety and efficacy of a low dose of flutamide (125 mg/day) in maintaining the clinical results already obtained using a higher dose (250 mg/day) was evaluated in 43 hirsute women who received 250 mg/day of flutamide as an initial treatment for 12 months and, subsequently, 125 mg/day of flutamide for an additional 12 months as a maintenance treatment. It was suggested that this therapeutic approach is a higly satisfactory method of management of the clinical signs of hyperandrogenism. In that study, during the initial treatment period, four subjects showed an increase of aspartate aminotransferase and alanine aminotransferase and dropped out (Venturoli *et al*. 2001). Lower dose, 125 mg/day, flutamide was also found to be effective in the treatment of hirsutism (Müderris and Bayram, 1999). Dodin *et al*. (1995) administered flutamide in a low dose of 125 mg twice daily for 12 months either alone in women with no risk of pregnancy or in combination with an oral contraceptive. They showed beneficial effects of a low dose of flutamide in women with idiopathic hirsutism. It was also found that the addition of an oral contraceptive reduced the recurrence of hirsutism after cessation of flutamide.

The authors have found that flutamide at 250 mg/day is an effective drug in the treatment of patients with hirsutism (Müderris *et al*., 1996). The effects of flutamide at 250 mg/day and 500 mg/day were also compared in the treatment of hirsutism in 65 patients with hirsutism and it was found that these two different doses of flutamide are similarly effective in reducing hair growth. There were no significant differences in any hormone levels during therapy in either groups (Müderris *et al*., 1997).

In another study, flutamide was given to 18 non-obese adolescent girls as 250 mg daily, and flutamide treatment was accompanied by a marked decrease in the hirsutism score, free androgen index, and testosterone, androstenedione, and DHEA levels and by an increase in SHBG concentrations. It was concluded that low-dose flutamide treatment is an effective and safe approach to reducing hirsutism and circulating androgen, low-density lipoprotein cholesterol, and triglyceride levels in girls with functional ovarian hyperandrogenism (Ibanez *et al*., 2000a).

Fatal and non-fatal hepatotoxicity has been reported infrequently in patients with prostate cancer and in women with hirsutism who are on flutamide (Gomez *et al*., 1992; Cusan *et al*., 1994). In another study, hepatotoxicity characterized by increase in transaminase levels occurred in one of 30 patients who were treated with 500 mg of flutamide per day. No hepatotoxicity was seen in the patients who were on 250 mg of flutamide per day (Müderris *et al*., 1997).

Flutamide is a very effective anti-androgen drug in the treatment of hirsutism. Liver function tests should be monitored regularly during the treatment period. Low-dose flutamide is relatively safe and effective.

Anti-androgen combinations

The anti-androgen drugs including spironolactone, CPA, finasteride and flutamide are effective in decreasing the hirsutism score. These drugs have different effects. Therefore, combining these anti-androgen drugs would be more effective than using one drug alone. For this reason, the effects and safety of different anti-androgen combinations in the treatment of patients with hirsutism has recently been investigated. Three of the combinations include Diane 35 (CPA plus ethyniloestradiol) and a different anti-androgen. The fourth one contains two different anti-androgens; spironolactone and finasteride. On the other hand, there could be many different anti-androgen combinations, such as spironolactone plus flutamide, flutamide plus finasteride.

Diane 35 and spironolactone combination

The clinical efficacy and safety of Diane 35 (cyproterone acetate, 2 mg, and ethinyloestradiol, 35 µg) plus spironolactone, 100 mg, combination and Diane 35 alone has been compared in the treatment of hirsutism in 50 women (Kelestimur and Sahin, 1998). Hirsutism score significantly decreased at the end of therapy for one year in both groups, but the reduction in hirsutism score in the women receiving Diane 35 plus spironolactone at 12 months was greater than in the women receiving Diane 35 alone. In other words, the percentage change in hirsutism score at 12 months was higher in the Diane 35 plus spironolactone group than in the Diane 35-alone group. It has also been found that the addition of spironolactone to Diane 35 may have a synergistic effect on hirsutism score. By combining Diane 35 with spironolactone, patients were treated with CPA, which possesses a powerful antigonadotrophic activity and anti-androgen effect, oestrogen and spironolactone. In other words, three drugs were given,

each with a different mechanism of action on androgens. Thus by this therapy it is possible to decrease concentrations of androgens, both of glandular and peripheral origin, and interfere with the interaction of dihydrotestosterone and its intracellular receptor (Kelestimur, 2001b).

Diane 35 and finasteride combination

There are two studies that have compared Diane 35 plus finasteride, 5 mg, combination and Diane 35 alone in the treatment of hirsutism (Tartagni *et al*. 2000; Sahin *et al*., 2001). The authors have compared Diane 35 plus finasteride, 5 mg, combination and Diane 35 alone in 34 women with hirsutism. In this study, it was found that the percentage reduction in hirsutism score in the Diane 35 plus finasteride group at 12 months was greater than in the Diane 35-alone group. The serum free testosterone significantly decreased at 12 months in the Diane 35 plus finasteride group. There were no significant differences between the total testosterone before and after the treatment with Diane 35 plus finasteride. SHBG levels were higher in both groups at 12 months. Obviously, oestrogen in Diane 35 increased SHBG levels which reduced the testosterone levels. By giving the combination of Diane 35 plus finasteride, the patient was treated with CPA, oestrogen and finasteride. Thus, it has been possible to decrease levels of androgens, both of glandular and peripheral origin, and inhibit the enzyme 5α-reductase.

In conclusion, the present data demonstrate that Diane 35 alone and Diane 35 plus finasteride 5 mg combination are effective and safe in the treatment of hirsutism. The percentage change in the Ferriman–Gallwey score at 12 months from baseline was higher in patients treated with Diane 35 plus finasteride than in patients treated with Diane 35 alone. Therefore, the addition of finasteride to Diane 35 has a synergistic effect on hirsutism score. In another study, Tartagni *et al*. (2000) compared the clinical efficacy of Diane 35 plus finasteride combination with Diane 35 alone in 50 women with hirsutism and they found that concurrent administration of finasteride and Diane 35 significantly decreased the hirsutism score. The duration of the treatment was 6 months, less than the authors' treatment period and they used a new therapeutic scheme: Diane 35 from day 1 to day 21, plus 5 mg of finasteride from day 1 to day 14. This and the authors' studies demonstrate that Diane 35 plus finasteride combination is effective, well accepted and safe in the treatment of hirsutism.

Diane 35 and flutamide combination

There is only one study looking at the effects of a flutamide plus Diane 35 combination. Taner *et al*. (2002) compared the effects of flutamide (250 mg/day) alone with a flutamide plus Diane 35 combination. They found that both therapies were similarly effective and safe in the treatment of hirsutism. The flutamide plus Diane 35 combination was better than flutamide alone in providing regular cycles (Taner *et al*., 2002). Both flutamide and CPA are hepatotoxic drugs and combination of these drugs may result in more liver toxicity. So, until there is enough data, this combination cannot be recommended.

Spironolactone and finasteride combination

One of the recent developments in the treatment of hirsutism is the combination of spironolactone and finasteride. A comparison has been made of the clinical efficacy and safety of the combination of spironolactone (100 mg/day) and finasteride (5 mg/day) with spironolactone (100 mg/day) alone in patients with hirsutism. It was found that the percentage decrease in the hirsutism score at 6 months was significantly higher in patients taking spironolactone and finasteride combination than in patients taking spironolactone alone. Surprisingly, the prevalence of polymenorrhoea in the spironolactone and finasteride combination group (20%) was lower than in the spironolactone-alone group (50%). In other words, the addition of finasteride to spironolactone leads to less frequent menstrual disturbances in women with hirsutism (Ünlühızarcı *et al*., 2002). The duration of the treatment was then extended to one year and it was shown that the mean percentage change in hirsutism scores from baseline in the spironolactone plus finasteride group (51.3%) was significantly higher than in the spironolactone-alone group (36.6%). The prevalence of polymenorrhoea in the spironolactone plus finasteride group (47.3%) was also lower than in the spironolactone-alone group (60.7%). There was no change in DHEA-S between before and after the treatment in either group, but spironolactone therapy resulted in a significantly increase in SHBG at the end of the treatment period. There is no clear explanation for the changes in SHBG due to spironolactone treatment. It seems that the spironolactone plus finasteride combination is effective and safe (Kelestimur *et al*., 2004).

Insulin sensitizers

The insulin-sensitizing drugs metformin and thiazolidinediones, including troglitazone and rosiglitazone, improve insulin resistance and reduce hyperinsulinaemia and hyperandrogenaemia in patients with PCOS. (Velazquez *et al*., 1994; Dunaif *et al*., 1996; Nestler and Jakubowicz, 1996; Ünlühızarcı *et al*., 1996; Moghetti *et al*., 2000b; Azziz *et al*., 2001; Fleming *et al*., 2002; Sahin *et al*., 2004). Moghetti *et al*. (2000b) reported that metformin reduces hyperinsulinaemia and hyperandrogenaemia, independently of changes in body weight. They found that higher plasma insulin, lower serum androstenedione, and less severe menstrual abnormalities are baseline predictors of clinical response to metformin. On the other hand, Stadtmauer *et al*. (2002) found that metformin use was beneficial in improving IVF outcomes in clomiphene-resistant PCOS patients. It seems that metformin is more effective in obese and insulin-resistant PCOS women. It has been suggested that obese women with PCOS should be screened for the metabolic syndrome, including glucose intolerance, with an oral glucose tolerance test (The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group, 2004).

The effects of insulin sensitizers on hirsutism score have recently been evaluated in a few studies. Most of these studies show that metformin is particularly effective on hirsutism score in PCOS women with obesity and/or insulin resistance. Kelly *et al*. (2002) investigated the effect of metformin on hirsutism in 10 women with PCOS. They found a significant improvement in hirsutism at the end of metformin treatment for 6 months compared with placebo. Metformin treatment

also reduced weight significantly and led to a significant improvement in cycle frequency. In another study including 32 obese women with PCOS, the effects of metformin and an ethinyloestradiol (35 μg)–cyproterone acetate (2 mg) combination were compared. The hirsutism score did not change during metformin treatment, but it decreased significantly in the subjects treated with the ethinyloestradiol (35 μg)–cyproterone acetate (2 mg) combination (Morin-Papunen *et al*., 2000).

In PCOS women with abdominal obesity, long-term treatment with metformin added to a hypocaloric diet induced, in comparison with placebo, a greated reduction of body weight and abdominal fat, particularly of the visceral depots, and a more consistent decrease of serum insulin, testosterone, and leptin concentrations. These changes were associated with a more significant improvement of hirsutism and menses abnormalities (Pasquali *et al*., 2000). Metformin treatment (500 mg three times per day) decreased the acne score by 14% ($P < 0.0005$) and slightly decreased the hirsutism score by 2.3% ($P < 0.05$). Metformin treatment was also associated with an improvement in menstrual regularity. Women with high DHEA-S exhibited less improvement of menstrual cycle regularity, no change in hirsutism, and an increase in levels of insulin-like growth factor I (IGF-I) after treatment (Kolodziejczyk *et al*., 2000).

Ibanez *et al*. (2000b) assessed the effects of metformin, given at a daily dose of 1275 mg for 6 months to 10 non-obese adolescent girls with hirsutism, ovarian hyperandrogenism, oligomenorrhoea, dyslipidemia, and hyperinsulinaemia. Metformin treatment was accompanied by a marked drop in hirsutism score, insulin response to an oral glucose tolerance test, free androgen index, and baseline testosterone, androstenedione, DHEA and DHEA-S. During metformin treatment, serum triglyceride, total cholesterol, and low-density lipoprotein cholesterol decreased and high-density lipoprotein cholesterol rose.

In a recent study, 52 patients with PCOS were randomized to receive either metformin 500 mg three times daily or dianette (ethinyloestradiol 35 μg; cyproterone acetate, 2 mg) treatment for 12 months. Both objective and subjective methods of evaluating hirsutism were used. The Ferriman–Gallwey score was significantly reduced after treatment in both groups. The degree of reduction in score was significantly greater in the metformin group (25%) compared with the dianette group (5%). The mean hair diameter was significantly reduced in both groups by a similar amount during the treatment period. The beneficial effects of metformin do not appear to be mediated by suppression of circulating androgens, which makes it possible that hyperinsulinaemia or related metabolic pathways may be important determinants of end-organ responses at the hair follicle. (Harborne *et al*., 2003).

The studies relating to the effects of metformin on hirsutism scores published so far are shown in **Table 2**. The number of patients in these studies was not high enough to conclude that metformin is significantly effective in the treatment of hirsutism. In a recent study, the effects of flutamide (250 mg daily), metformin (1275 mg daily) and flutamide–metformin combination have been compared in young, non-obese women with hyperinsulinaemic hyperandrogenism, and combined treatment was found to have additive effects on insulin sensitivity, hyperandrogenaemia, and dyslipidaemia. The combined treatment also significantly decreased hirsutism score (Ibanez *et al*., 2002).

Troglitazone improves ovulatory dysfunction, hirsutism, hyperandrogenaemia, and insulin resistance of PCOS in a dose-related fashion, with a minimum of adverse effects. It has been speculated that these clinical improvements result from attenuation of the associated insulin resistance, hyperinsulinaemia, and hyperandrogenism. When treated with troglitazone, 600 mg daily, hirsute PCOS patients experienced a 15% decrease in Ferriman–Gallwey score by 20 weeks of therapy (Azziz *et al*., 2001). Because of liver toxicity troglitazone is not available in the market.

Not enough data exist regarding the effects of rosiglitazone and pioglitazone on hirsutism. It seems that insulin sensitizers have beneficial effects in the treatment of hirsutism. In

Table 2. The effects of metformin on hirsutism score.

References	*Duration (months)*	*Dose (mg/day)*	*No. of subjects*	*Hirsutism score (before treatment)*	*(after treatment)*	P-*value*
Kolodziejczyk *et al*. (2000)	3	1500	35	8.11 ± 0.73[a]	7.86 ± 0.7	<0.05
Kelly *et al*. (2002)	6	1500	10	17.7 ± 1.4[b]	15.8 ± 1.4	<0.002
Ibanez *et al*. (2000b)	6	1275	10	16.6 ± 1.4[b]	10.7 ± 1.3	<0.001
Morin-Papunen *et al*. (2000)	6	1000–2000	8	10.3 ± 1.9[c]	10.0 ± 1.9	NS
Pasquali *et al*. (2000)	6	1750	10	14.8 ± 7.5[b]	12.9 ± 7.6	<0.05
Harborne *et al*. (2003)	12	1500	18	20.3 (17.8–22.9)[b,f]	–[e]	<0.01
Harborne *et al*. (2003)	12	1500	18	79[d]	69	<0.004

NS: non-significant.
[a]Modified Thomas–Ferriman scale (Thomas and Ferriman, 1957).
[b]Ferriman–Gallwey score (Ferriman and Gallwey, 1961).
[c]Not stated.
[d]Combined hair diameter (μm).
[e]Insufficient data after metformin treatment but 25% reduction in hirsutism score from baseline was found after treatment.
[f]Confidence limits given in parentheses.

particular they would be more effective in hirsute patients with insulin resistance. On the other hand, metformin could be combined with anti-androgen drugs. Further studies are required to evaluate the role of insulin sensitizers in patients with hirsutism.

Conclusion

In recent years, there have been remarkable developments in the medical treatment of hirsutism in terms of safety, efficacy and cost-effectiveness. Low-dose flutamide (250 mg/day) and low-dose finasteride (2.5 mg/day) are just as effective as high-dose flutamide (500 mg/day) and high-dose finasteride (5 mg/day). Similarly, high-dose CPA (50 mg) is not better than low-dose CPA (2 mg). Low-dose treatment is obviously well-tolerated with a reduced cost for the patient with hirsutism. In particular, low-dose anti-androgen drugs may be administered for the long-term maintenance therapy that is required in most patients to prevent recurrence of symptoms. Combination therapies including oral contraceptives with anti-androgen agents, Diane 35 with anti-androgen agents or different anti-androgens with each other are more effective than a single agent in the treatment of hirsutism. The combination of anti-androgen drugs with different mechanisms of action may be an alternative therapy in the treatment of hirsutism. Insulin sensitizers, particularly metformin, is very promising for the treatment of hirsutism, but more data are needed about their efficacy and the effectiveness of anti-androgen plus metformin combinations. Pregnancy should be prevented during treatment with anti-androgen drugs because the male fetus is at risk of abnormal development. One anti-androgen drug or combined treatment may be effective in one patient but may be ineffective in another, so anti-androgen treatment should be individualized and the underlying cause should be clarified as well as possible. It seems that insulin sensitizers are more effective in patients with insulin resistance.

References

Azziz R, Ehrmann D, Legro RS *et al*. 2001 Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. *Journal of Clinical Endocrinology and Metabolism* **86**, 1626–1632.

Barth JH, Cherry CA, Wojnarowska F, Dawber RPR 1991 Cyproterone acetate for severe hirsutism: results of a double-blind dose ranging study. *Clinical Endocrinology* **35**, 5–10.

Bayram F, Müderris II, Sahin Y, Kelestimur F 1999 Finasteride treatment for one year in 35 hirsute patients. *Experimental and Clinical Endocrinology and Diabetes* **107**, 195–197.

Bayram F, Müderris II, Güven M, Kelestimur F 2002 Comparison of high-dose finasteride (5 mg/day) versus low-dose (2.5 mg/day) finasteride in the treatment of hirsutism. *European Journal of Endocrinology* **147**, 467–471.

Bayram F, Müderris I, Güven M *et al*. 2003 Low-dose (2.5 mg/day) finasteride treatment in hirsutism. *Gynecological Endocrinology* **17**, 419–422.

Castello M, Tosi F, Perrone F *et al*. 1996 Outcome of long-term treatment with the 5α-reductase inhibitor finasteride in idiopathic hirsutism: clinical and hormonal effects during a year course of therapy and 1-year follow-up. *Fertility and Sterility* **66**, 734–740.

Cesur V, Kamel N, Uysal AZ *et al*. N 1994 The use of antiandrogen flutamide in the treatment of hirsutism. *Endocrine Journal* **41**, 573–577.

Conn JJ, Jacobs HS 1997 The clinical management of hirsutism. *European Journal of Endocrinology* **136**, 339–348.

Cusan L, Dupont A, Gomez JL *et al*. 1994 Comparison of flutamide and spironolactone in the treatment of hirsutism: a randomized controlled trial. *Fertility and Sterility* **61**, 281–287.

Dallob AL, Sadick NS, Unger W *et al*. 1994 The effect of finasteride, a 5α-reductase inhibitor, on scalp skin testosterone and dihydrotestosterons concentrations in patients with male pattern baldness. *Journal of Clinical Endocrinology and Metabolism* **79**, 703–706.

Dodin S, Faure N, Cedrin I *et al*. 1995 Clinical efficacy and safety of low-dose flutamide alone and combined with an oral contraceptive for the treatment of idiopathic hirsutism. *Clinical Endocrinology* **43**, 575–582.

Dunaif A, Scott D, Finegood D *et al*. 1996 The insulin-sensitizing agent troglitazone improves metabolic and reproductive abnormalities in the polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism* **81**, 3299–3306.

Erenus M, Gürbüz O, Durmusoglu F *et al*. 1994 Comparison of the efficacy of spironolactone versus flutamide in the treatment of hirsutism. *Fertility and Sterility* **61**, 613–616.

Erenus M, Yücelten D, Durmusoglu F *et al*. 1997 Comparison of finasteride versus spironolactone in the treatment of idiopathic hirsutism. *Fertility and Sterility* **68**, 1000–1003.

Falsetti L, Gambera A 1999 Comparison of finasteride and flutamide in the treatment of idiopathic hirsutism. *Fertility and Sterility* **72**, 41–46.

Falsetti L, Rosina B, De Fusco D 1998 Serum levels of 3α-androstanediol glucuronide in hirsute and non hirsute women. *European Journal of Endocrinology* **138**, 421–424.

Falsetti L, Gambera A, Legrenzi L *et al*. 1999 Comparison of finasteride versus flutamide in the treatment of hirsutism. *European Journal of Endocrinology* **141**, 361–367.

Farquhar C, Leo O, Toomath R, Jepson R 2001 Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. *Cochrane Database of Systematic Reviews* **4**, CD000194.

Ferriman D, Gallwey JD 1961 Clinical assessment of body hair growth in women. *Journal of Clinical Endocrinology and Metabolism* **21**, 1440–1448.

Fleming R, Popkinson ZE, Wallace AM, *et al*. 2002 Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. *Journal of Clinical Endocrinology and Metabolism* **87**, 569–574.

Fruzzetti F, de Lorenzo D, Parrini D, Ricci C 1994 Effects of finasteride, a 5α-reductase inhibitor, on circulating androgens and gonadotropin secretion in hirsute women. *Journal of Clinical Endocrinology and Metabolism* **79**, 831–835.

Fruzzetti F, Bersi C, Parrini D *et al*. 1999 Treatment of hirsutism: comparisons between different antiandrogens with central and peripheral effects. *Fertility and Sterility* **71**, 445–451.

Girard J, Baumann JB, Buhler U *et al*. 1978 Cyproterone acetate and ACTH adrenal function. *Journal of Clinical Endocrinology and Metabolism* **47**, 581–585.

Gomez JL, Dupont A, Cusan L *et al*. 1992 Incidence of liver toxicity associated with the use of flutamide in prostate cancer patients. *American Journal of Medicine* **92**, 465–470.

Harborne L, Fleming R, Lyall H *et al*. 2003 Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism* **88**, 4116–4123.

Ibanez L, Potau N, Marcos MV, de Zegher F 2000a Treatment of hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism in non-obese, adolescent girls: effect of flutamide. *Journal of Clinical Endocrinology and Metabolism* **85**, 3251–3255.

Ibanez L, Valls C, Potau N *et al*. 2000b Sensitization to insulin in adolescent girls to normalize hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism after precocious pubarche. *Journal of Clinical Endocrinology and Metabolism* **85**, 3526–3530.

Ibanez L, Valls C, Ferrer A *et al*. 2002 Additive effects of insulin-sensitizing and anti-androgen treatment in young, non-obese women with hyperinsulinism, hyperandrogenism, dyslipidemia,

and anovulation. *Journal of Clinical Endocrinology and Metabolism* **87**, 2870–2874.

Kelestimur F 2001a Hirsutism of adrenal origin in adolescents: consequences in adults. *Journal of Pediatric Endocrinology and Metabolism* **14**, 1309–1315.

Kelestimur F 2001b Diane 35 and spironolactone combination in the treatment of hirsutism. *Clinical Endocrinology* **54**, 699.

Kelestimur F, Sahin Y 1998 Comparison of Diane 35 and Diane 35 plus spironolactone in the treatment of hirsutism. *Fertility and Sterility* **69**, 66–69.

Kelestimur F, Sahin Y, Ayata D, Tutus A 1996 The prevalence of non-classical adrenal hyperplasia due to 11β-hydroxylase deficiency among hirsute women in a Turkish population. *Clinical Endocrinology* **45**, 381–384.

Kelestimur F, Everest H, Ünlühızarcı K *et al*. 2004 A comparison between spironolactone plus finasteride and spironolactone in the treatment of hirsutism. *European Journal of Endocrinology* **150**, 351–354.

Kelly CJG, Gordon D 2002 The effect of metformin on hirsutism in polycystic ovary syndrome. *European Journal of Endocrinology* **147**, 217–221.

Kolodziejczyk B, Duleba AJ, Spaczynski RZ, Pawelczyk L 2000 Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. *Fertility and Sterility* **73**, 1149–1154.

Lobo RA, Shoupe D, Serafini P *et al*. 1985 The effects of two doses of spironolactone on serum androgens and anagen hair in hirsute women. *Fertility and Sterility* **43**, 200–205.

Lumachi F, Rondinone R 2003 Use of cyproterone acetate, finasteride, and spironolactone to treat idiopathic hirsutism. *Fertility and Sterility* **79**, 942–946.

Mallari R, Sinclair RD 2002 Shortness of breath: an uncommon side-effect of cyproterone acetate in the treatment of androgenetic alopecia. *International Journal of Dermatology* **41**, 946–947.

Marugo M, Bernasconi D, Meozzi M *et al*. 1994 The use of flutamide in the management of hirsutism. *Journal of Endocrinological Investigation* **17**, 195–199.

McMullen GR, Van Herle AJ 1993 Hirsutism and the effectiveness of spironolactone in its management. *Journal of Endocrinological Investigation* **16**, 925–932.

Moghetti P, Castello R, Mognani CM *et al*. 1994 Clinical and hormonal effects of the 5α-reductase inhibitor finasteride in idiopathic hirsutism. *Journal of Clinical Endocrinology and Metabolism* **79**, 1115–1121.

Moghetti P, Tosi F, Tosti A *et al*. 2000a Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial. *Journal of Clinical Endocrinology and Metabolism* **85,** 89–94.

Moghetti P, Castello R, Negri C *et al*. 2000b Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *Journal of Clinical Endocrinology and Metabolism* **85**, 139–146.

Morin-Papunen LC, Vauhkonen I, Koivunen RM *et al*. 2000 Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism* **85**, 3161–3168.

Müderris II, Bayram F 1999 Clinical efficacy of lower dose flutamide 125 mg/day in the treatment of hirsutism. *Journal of Endocrinological Investigation* **22**, 165–168.

Müderris II, Bayram F, Sahin Y *et al*. 1996 The efficacy of flutamide 250 mg/day in the treatment of patients with hirsutism. *Fertility and Sterility* **66**, 220–222.

Müderris II, Bayram F, Sahin Y, Kelestimur F 1997 A comparison between two doses of flutamide (250 mg/d and 500 mg/d) in the treatment of hirsutism. *Fertility and Sterility* **68**, 644–647.

Nestler JE, Jakubowicz DJ 1996 Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome *New England Journal of Medicine* **335**, 617–623.

Pasquali R, Gambineri A, Biscotti D *et al*. 2000 Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism* **85**, 2767–2774.

Pazos F, Escobar-Morreale HF, Balsa J, *et al*. 1999 Prospective randomized study comparing the long-acting gonadotropin-releasing agonist triptorelin, flutamide, and cyproterone acetate, used in combination with an oral contraceptive, in the treatment of hirsutism. *Fertility and Sterility* **71**, 122–128.

Rittmaster RS 1995 Finasteride. *New England Journal of Medicine* **330**, 120–125.

Rittmaster RS 1999 Antiandrogen treatment of polycystic ovary syndrome. *Endocrinology Clinics of North America* **28**, 409–421.

Rubens R 1984 Androgen levels during cyproterone acetate and ethinyl oestradiol treatment of hirsutism. *Clinical Endocrinology* **20**, 313–325.

Sahin Y, Kelestimur F 1997 The frequency of late-onset 21-hydroxylase and 11β-hydroxylase deficiency in women with polycystic ovary syndrome. *European Journal of Endocrinology* **137**, 670–674.

Sahin Y, Kelestimur F, Bayram F, Müderris I 1998 Comparison of cyproterone acetate plus ethinyl estradiol and finasteride in the treatment of hirsutism. *Journal of Endocrinological Investigation* **21**, 348–352.

Sahin Y, Kelestimur F, Dilber S 2001 Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism. *Fertility and Sterility* **75**, 496–500.

Sahin Y, Yirmibes Ü, Kelestimur F, Aygen E 2004 The effects of metformin on insulin resistance, clomiphen-induced ovulation and pregnancy rates in women with polycystic ovary syndrome. *European Journal of Obstetrics and Gynecology and Reproductive Biology* in press.

Seaman HE, Vries CS, Farmer RD 2003 The risk of venous thromboembolism in women prescribed cyproterone acetate in combination with ethinylestradiol: a nested cohort analysis and case-control study. *Human Reproduction* **18**, 522–526.

Stadtmauer LA, Toma SK, Riehl RM, Talbert LM 2002 Impact of metformin therapy on ovarian stimulation and outcome in 'coasted' patients with polycystic ovary syndrome undergoing in-vitro fertilization. *Reproductive BioMedicine Online* **5**, 2112–2116.

Taner C, Inal M, Basogul A *et al*. 2002 Comparison of the clinical efficacy and safety of flutamide versus flutamide plus an oral contraceptive in thr treatment of hirsutism. *Gynecologic and Obstetric Investigation* **54**, 105–108.

Tartagni M, Schonauer LM, De Salvia M *et al*. 2000 Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism. *Fertility and Sterility* **73**, 718–723.

The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group 2004 Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and Sterility* **81**, 19–25.

Thomas PK, Ferriman DG 1957 Variation in facial and pubic hair growth in white women. *American Journal of Physical Antropology* **15**, 171–180.

Ünal A, Sahin Y, Kelestimur F 1993 Acromegaly with polycystic ovaries, hyperandrogenism, hirsutism, insulin resistance and acathosis nigricans: A case report. *Endocrine Journal* **40**, 207–211.

Ünlühızarcı K, Kelestimur F, Bayram F *et al*. 1996 The effects of metformin on insulin resistance in women with polycystic ovary syndrome. *Clinical Endocrinology* **51**, 231–236.

Ünlühızarcı K, Everest H, Bayram F, Kelestimur F 2002 Comparison of spironolactone and spironolactone plus finasteride in the treatment of hirsutism. *Fertility and Sterility* **78**, 1331–1333.

Velazquez EM, Mendoza S, Hamer T *et al*. 1994 Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin

resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. *Metabolism* **43**, 647–654.

Venturoli S, Paradisi R, Bagnoli A *et al*. 2001 Low-dose flutamide (125 mg/day) as maintenance therapy in the treatment of hirsutism. *Hormone Research* **56**, 25–31.

Wong IL, Morris RS, Chang L *et al*. 1995 A prospective randomized trial comparing finasteride to spironolactone in the treatment of hirsute women *Journal of Clinical Endocrinology and Metabolism* **80**, 233–238.

Paper based on contribution presented at the 'PCOS Symposium: Current Concepts, Treatment and Ovulation Induction' in Antalya, Turkey, September 2003.

Received 9 January 2004; refereed 3 February 2004; accepted 10 March 2004.