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The metabolic effects of drugs used for the treatment of polycystic ovary syndrome

Polikistik over sendromu tedavisinde kullanılan ilaçların metabolik etkileri

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age. It is characterized by menstrual disorders, hyperandrogenism (clinical and/or biochemical) and ultrasonographic features. It is well known that PCOS has unfavourable effects on carbohydrate metabolism, the parameters of cardiovascular disease and lipid profile. Mode of treatment is mainly guided by the main complaint of the patient. A lot of medicines have been used for many years to treat these women. For that reason the recognition the effects of these drugs on the metabolic risk profile is important. The aim of this review was to evaluate the effects of these drugs on metabolic parameters in women with PCOS.

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Key words: Polycystic ovary syndrome, treatment, drug effects; metabolic parameter

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Özet

Polikistik over sendromu (PKOS), üreme çağındaki kadınlarda en sık görülen endokrin bozukluktur. Menstruel bozukluklar, hiperandrojenizm (klinik ve/veya biyokimyasal) ve ultrasonografik özellikleriyle karakterizedir. PKOS'nun karbonhidrat metabolizması, kardiyovasküler hastalık parametreleri ve lipid profili üzerine olan olumsuz etkileri iyi bilinmektedir. Tedavi şekli genelde hastanın asıl yakınmasına göre düzenlenir. Bu kadınların tedavisinde uzun yıllardan beri çeşitli ilaçlar kullanılmaktadır. Bu nedenle de tedavide kullanılan bu ilaçların, metabolik risk profili üzerine olan etkilerini bilmek önemli hale gelmektedir. Bu derlemenin amacı tedavide kullanılan bu ilaçların, PKOS'lu bayanların metabolik parametreleri üzerine olan etkilerini değerlendirmektir. (J Turkish-German Gynecol Assoc 2013; 14: 168-73)

Anahtar kelimeler: Polikistik over sendromu, tedavi, ilaç etkileri, metabolik parametre

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, and is characterized by anovulation, hyperandrogenemia, obesity and insulin resistance (1-3).

PCOS was defined by Stein and Leventhal for the first time in 1935 as hyperandrogenemia, menstrual irregularity, large polycystic ovaries and obesity (4). The Rotterdam criteria, which we currently use frequently in PCOS diagnosis, were defined in 2003 (5). These criteria include; polycystic ovaries seen by ultrasound; ≥12 follicles in each ovary with a diameter of 2-9 mm and/or increase in the ovarian volume (>10 cm^3), chronic oligo-anovulation and hyperandrogenemia (determined clinically or in the laboratory). Other diseases should be excluded and at least two of these three criteria should be present to make a diagnosis. The PCOS criteria were rearranged by the Androgen Excess Society in 2009; these include androgen excess (clinical and/or biochemical hyperandrogenism), ovarian dysfunction (oligo-anovulation and/or polycystic ovarian morphology) and exclusion of other diseases with hyperandrogenism and exclusion of ovulatory diseases (6). The Androgen Excess Society recommends that all three criteria should be present for a diagnosis of PCOS.

The prevalence of the syndrome has been reported to be approximately 6-8% (7). The ultrasonographic prevalence of PCOS ranges between 14% and 23% (8, 9). There are no differences in PCOS prevalence in terms of ethnic background (10). The etiology of PCOS is not exactly known. Genetic and environmental factors have been blamed. The frequencies of hyperandrogenism and menstrual dysfunction are increased in the mothers and sisters of patients with PCOS. Serum androgen levels are increased in the fathers and brothers of patients with PCOS (11). Different studies in which potential genetic defects which might be involved in development of PCOS were examined showed that the syndrome is a complex polygenic defect (12). No specific environmental factors have been defined, but obesity is especially emphasized. The frequency of obesity in PCOS has been reported to be 40-60% (13). Obesity increases the prevalence of PCOS (14).

Three theories are emphasized in its pathophysiology. These include hypothalamic-pituitary dysfunction, ovarian hyper-

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androgenism and peripheral insulin resistance. Intraovarian androgen excess is responsible of both anovulation and the development of numerous follicle cysts. According to the abnormal pituitary function hypothesis, the increase in the frequency and amplitude of pulsatile secretion of LH increases androgen production in the ovaries. This results in discontinued follicle development (15). In addition, increased androgen blocks the inhibitory action of progesterone on the hypophysis. According to the hypothesis of ovarian hyperandrogenism, mainly primary functional ovarian hyperandrogenism is involved in PCOS (16). In vitro studies have shown an abnormal steroidogenic phenotype in isolated theca cell culture (17). According to the third hypothesis, insulin resistance and hyperinsulinemia are important factors in steroidogenic dysfunction in PCOS (18, 19). Insulin resistance and hyperinsulinemia stimulate androgen synthesis in the ovaries and lead to an increase in the levels of free testosterone by decreasing the synthesis of sex hormone binding globulin (SHBG) in the liver. Insulin resistance also contributes to the development of metabolic syndrome. Metabolic syndrome is present in 25% of adolescent PCOS cases and in 40% of adults aged 40 years with PCOS (20-23). One third of PCOS patients have an abnormal glucose tolerance test and 10% have type 2 diabetes mellitus (24).

PCOS generally presents with menstrual irregularity (oligoamenorrhea, dysfunctional uterine bleeding), hyperandrogenism findings (hirsutism, acne, oily skin, androgenic alopecia), infertility and obesity. Other clinical conditions related to PCOS include impaired glucose tolerance (IGT), type 2 diabetes mellitus (24), metabolic syndrome (20-23), non-alcoholic steatohepatitis (14), sleep apnea syndrome (25), malignancy (endometrium, ovary, breast cancer) (14, 26) and increased cardiovascular risk (27-29). An atherogenic lipid profile is observed as a result of increased LDL cholesterol, increased triglyceride levels and decreased HDL cholesterol levels in these patients (30-32).

Since the etiopathogenesis of PCOS is not clearly known, current treatment options are generally symptomatic. Two categories are emphasized in treatment. These include treatment of anovulatory infertility and treatment of the symptoms related to PCOS (menstrual dysfunction, hirsutism, infertility, etc.). The first step in the treatment of the symptoms related to PCOS includes lifestyle changes and weight loss, if the patient is obese. Medical treatment includes combined oral contraceptives (COC), spironolactone, finasteride, flutamide, metformin and combinations of these treatments.

COCs contain a progestin and ethinyl estradiol, which is a synthetic estrogen. Many of these progestins (levonorgestrel, norgestrel, desogestrel, gestodene, noretindrone) are derivatives of testosterone and show androgenic properties (33). Drospienone and cyproterone acetate (CPA), which are among the other progestins, are not structurally related to testosterone and show antiandrogenic activity. CPA blocks androgen receptors and inhibits 5-α-reductase activity (34). Thus, the serum androgen level is decreased. Drospirenone decreases blood pressure with its anti-mineralocorticoid action in addition to its anti-androgenic property. Conclusively, CPA and COCs which contain drospirenone suppress ovarian androgen production by inhibiting LH secretion, decrease serum free testosterone levels by increasing the synthesis of SHBG in the liver, block androgen receptors and thus regular menstruation, and prevent endometrial hyperplasia such that a decrease in the risk of endometrial cancer and regression of hirsutism are observed.

Spironolactone is an aldosterone antagonist, and its action is dependent on the dose. It is a competitive inhibitor of androgen receptors and also inhibits the activity of 5-α-reductase. Finasteride inhibits the activity of 5α-reductase and is less effective compared to the other anti-androgens (35). Flutamide is an androgen receptor blocker. Its efficiency is similar to spironolactone (36).

Metformin decreases ovarian androgen production by decreasing the serum insulin level and mitigating insulin resistance (37). Thus, the serum testosterone level decreases, the hirsutism score and menstrual dysfunction improve and infertility is reversed (38).

The negative effects of PCOS on carbohydrate metabolism, cardiovascular disease parameters and the lipid profile are well-known. Therefore, it becomes important to know the effects of the drugs used commonly in PCOS treatment on the metabolic risk profile.

Metabolic effects of drugs

COCs have been used in the treatment of PCOS for more than 30 years. There are various studies evaluating the effects of COCs on carbohydrate metabolism, the lipid profile and cardiovascular risk parameters.

Morin-Papunen et al. (39) compared the metabolic and endocrine effects of metformin and an oral contraceptive tablet (Diane 35) containing ethinyl estradiol (35 μg) and cyproterone acetate (CPA) (2 mg) in obese women with PCOS. Eighteen patients with a body mass index (BMI) above 27 were included in the study. Eight patients were given metformin and ten patients were given an oral contraceptive tablet for 6 months; the effects were evaluated at the beginning and at the end of the treatment period. The waist/hip ratio, as well as the serum free fatty acid, fasting insulin and fasting blood glucose levels decreased significantly in the group who received metformin ($p<0.05$), and impaired fasting glucose (IFG) returned to normal in one patient. The menstrual cycle improved, but the hirsutism score did not change in these patients. In the group who received Diane 35, the waist/hip ratio, serum free fatty acids, fasting insulin and fasting blood glucose did not change. One patient showed progression from IFG to diabetes mellitus and IGT developed in three patients. The menstrual cycle improved and hirsutism score decreased in the patients given Diane 35.

Mastorakos et al. (40) compared the effects of two different COCs on androgen and lipid parameters in patients with PCOS; 30 μg ethinyl estradiol + 0.15 mg desogestrel were given to group A (n=14) and 35 μg ethinyl estradiol + 2 mg cyproterone acetate were given to group B (n=14) for 12 months and the findings were compared at the beginning and at the end of the treatment period. In both groups, total and free testosterone levels decreased, the hirsutism score was reduced, total cholesterol (TC), LDL and HDL increased, the TC/HDL and LDL/HDL ratios did not change and a significant increase was found in TG levels in group B compared to group A.

In another study performed by Mastorakos et al. (41), the effects of two different COCs on carbohydrate metabolism were evaluated; 30 μg ethinyl estradiol + 0.15 mg desogestrel were given to group A (n=18) and 35 μg ethinyl estradiol + 2 mg cyproterone acetate were given to group B (n=18) for 12 months and the findings were compared at the beginning and at the end of the treatment period. In both groups, insulin resistance increased. The fasting blood glucose/insulin ratio decreased and first and second phase insulin secretion in OGTT was increased in group B. Conclusively, oral contraceptive drugs led to a change in insulin sensitivity. In addition, cyproterone acetate was related to an increase in insulin secretion and hyperinsulinemia.

Orbetsova et al. (42) evaluated anti-androgens and the effects of combinations of anti-androgens and insulin sensitizing agents on metabolic and hormonal parameters in women with PCOS. Forty-four patients were included in the study and divided into three groups. Diane 35 was given to the first group, Diane 35 + metformin were given to the second group and Diane 35 + rosiglitazone were given to the third group for 6 months. The body weight, body fat mass and abdominal fat distribution did not change in the first group. Despite mild hyperinsulinemic action, no change was found in carbohydrate tolerance. Negative effects were observed on atherogenic lipids. In the second group, the body fat mass and abdominal fat distribution decreased, blood glucose levels did not change, insulin levels decreased, diastolic blood pressure decreased and a positive effect was observed on HDL, while a neutral effect was observed on atherogenic lipids. In the third group, the body fat mass and abdominal fat distribution did not change, fasting blood glucose did not change, fasting insulin levels and the Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) decreased and a neutral effect was observed on atherogenic lipids.

In a meta-analysis comparing the efficiency of placebo with thiazolidinediones in PCOS (43), it was shown that thiazolidinediones decreased insulin and fasting blood glucose levels, but were not efficient in decreasing the Ferriman-Gallwey score and androgen levels and led to weight gain.

Gode et al. (44) evaluated the effects of ethinyl estradiol + cyproterone acetate on cardiovascular risk parameters. 40 patients were given a COC containing cyproterone acetate for 6 months. At the end of the treatment period, TC, LDL and TG increased compared to the baseline values ($p<0.05$). A significant increase was found in the carotid intima-media thickness (0.03±0.01 mm) ($p<0.05$). Brachial artery flow-mediated dilatation was observed to be decreased ($p<0.05$).

In a study in which the effects of medical treatment on endothelial function and insulin resistance were evaluated in patients with PCOS (45), one group was given metformin (n=36) and the other group (n=30) was given 35 μg ethinyl estradiol + 2 mg cyproterone acetate for 6 months. The effects were compared at the beginning and at the end of the treatment period. Glucose and insulin levels were evaluated using the oral glucose tolerance test. In the group who received metformin, the insulin, high sensitivity C-reactive protein (HS-CRP) and HDL levels decreased and brachial artery flow-mediated dilatation increased. In the group who received COC, the insulin, HS-CRP, glucose, SHBG and TG levels increased, while plasminogen activator inhibitor-1, LDL and testosterone levels decreased.

Ozkaya et al. (46) gave metformin twice a day to 19 women with PCOS for 3 months. The effects were evaluated at the beginning and at the end of the treatment period. Fasting insulin, free testosterone, dehydroepiandrosterone sulfate and visfatin levels decreased. HOMA-IR, BMI and waist circumference values also decreased. The changes in TC, HDL, LDL, TG and prolactin concentrations were not significant.

Kriplani et al. (47) investigated the effects of two different COCs on clinical and biochemical parameters in patients with PCOS. Group A was given (n=30) 30 μg ethinyl estradiol + 3 mg drospirenone and group B was given (n=30) 30 μg ethinyl estradiol + 0.15 mg desogestrel for 6 months and the effects were compared at the beginning and at the end of the treatment period. In group A, LDL decreased, HDL increased, fasting blood glucose, postprandial blood glucose and insulin level decreased, the hirsutism score improved and systolic-diastolic blood pressure decreased. In group B, fasting blood glucose, postprandial blood glucose and insulin level increased, the hirsutism score did not change, and systolic and diastolic blood pressure increased. Conclusively, it was interpreted that drospirenone was more efficient compared to the COC containing desogestrel because of its positive anti-androgenic effects on menstrual cycle regularity, blood pressure and lipid profile.

In a different study (48), 30 μg ethinyl estradiol + 3 mg drospirenone were given to 20 women with PCOS for 6 months. When the effects were evaluated at the beginning and at the end of the treatment period, it was found that testosterone levels decreased, SHBG levels increased and the hirsutism score improved, while no significant effects were observed on carbohydrate metabolism (FBG, fasting insulin, HOMA IR).

In a study where the effect of COC on body composition was evaluated in patients with PCOS (49), 30 μg ethinyl estradiol + 3 mg drospirenone were given to patients for 6 months. After 6 months of treatment, no changes were observed in body weight, BMI and waist/hip ratio, while a significant increase was found in the total fat percentage and central fat percentage. While the lipid parameters were increased (TC, LDL, TG, HDL), no changes were observed in insulin resistance and glucose metabolism.

Nakhjavani et al. (50) gave 100 mg spironolactone to 27 patients (20 PCOS + 7 idiopathic hirsutism) for 3 months and evaluated the lipid profile. Testosterone, dehydroepiandrosterone sulfate and prolactin levels decreased. TC, TG and FBG levels did not change. LDL, TC/HDL increased, while HDL decreased.

In a study which compared the efficiencies of spironolactone and metformin (51), group A (n=34) was given 50 mg/day spironolactone and group B (n=35) was given 1000 mg/day metformin for 6 months. In both groups, improvements were observed in the menstrual cycle, hirsutism score, glucose tolerance and HOMA-IR. The LH/FSH ratio and testosterone levels decreased. The blood pressure, BMI and waist/hip ratio did not

Table 1. Metabolic effects of the drugs used to treat PCOS

	Carbohydrate metabolism	Lipid profile	Hormonal profile	Hirsutism score	Menstrual dysfunction
Metformin	positive	positive	positive or neutral	positive or neutral	positive
Cyproterone acetate	negative	negative	positive	positive	positive
Drospirenone	positive or neutral	positive	positive	positive	positive
Desogestrel	negative	negative	positive or neutral	positive or neutral	positive
Spironolactone	positive or neutral	negative	positive	positive	positive

change. Conclusively, it was interpreted that both drugs were efficient in the treatment of PCOS, but spironolactone was superior to metformin in the treatment of hirsutism, menstrual imbalance and hormonal imbalance with a slight increase in side effects.

In a meta-analysis which evaluated the efficiency of exercise treatment in PCOS (52), the results of eight studies which included moderate physical activity and exercise periods ranging between 12 and 24 weeks were assessed. A 4.5-10% decrease in body weight, a 9-30% improvement in insulin resistance and improved ovulatory functions were observed with exercise. This was found to be independent of the type of exercise and the frequency and time of the sessions.

In summary, these studies generally show that cyproterone acetate has favorable effects on menstrual dysfunction, hirsutism score and hormonal profile and unfavorable effects on the lipid profile, carbohydrate metabolism and cardiovascular risk parameters. Drospirenone has favorable effects on menstrual dysfunction, hirsutism score, hormonal profile, carbohydrate metabolism, lipid profile and blood pressure. Spironolactone has favorable or neutral effects on carbohydrate metabolism, favorable effects on hirsutism score and hormonal profile and unfavorable effects on the lipid profile. Metformin has favorable effects on carbohydrate metabolism, menstrual dysfunction, lipid profile and favorable or neutral effects on the hormonal profile and hirsutism score (Table 1).

Conclusion

PCOS is a metabolic disease which has unfavorable effects on the lipid profile, carbohydrate metabolism and cardiovascular risk parameters. It has been shown that some drugs which are used in treatment of PCOS also have unfavorable effects on these parameters. Therefore, the metabolic effects of the drugs should be considered in treatment selection.

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