Does obesity diminish the positive effect of oral contraceptive treatment on hyperandrogenism in women with polycystic ovarian syndrome?

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Polycystic ovarian syndrome (PCOS) is an obvious indication for long-term treatment. Combined oral contraceptives (COC) remain the first choice for the treatment of hyperandrogenism in most patients. However, differences in endocrine and metabolic parameters between obese and lean patients have been postulated. This is the first study evaluating the effect of COC treatment in obese versus non-obese PCOS patients. In total, 28 lean [body mass index (BMI) <25 kg/m²] and 15 obese (BMI >30 kg/m²) women patients were enrolled in the study. The concentrations of androgens, sex hormone-binding globulin (SHBG) and lipids were measured before and after 6 months of treatment with COC containing low-androgenic progestins. Clinical androgenic symptoms were monitored. There was a lower concentration of SHBG in obese patients, but there were no differences in androgen concentrations between both groups before the study. Highly significant changes in concentrations of testosterone ($P < 0.001$), androstenedione ($P < 0.0001$), SHBG ($P < 0.001$) and LH ($P = 0.01$) were demonstrated in lean patients, with only less significant changes in SHBG ($P < 0.01$) and testosterone ($P < 0.05$) in obese patients during the study. Clinical androgenic symptoms improved significantly ($P = 0.05$) only in the group of lean women. No reduction in low-density lipoprotein-cholesterol/high-density lipoprotein-cholesterol ratio was observed in either group. In conclusion, the positive effect of COC treatment on androgen production, serum androgen binding capacity, and clinical androgenic symptoms was negatively influenced by an increased BMI.

Key words: androgens/lipids/obesity/oral contraceptives/polycystic ovarian syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is an evident indication for long-term treatment as a proven risk factor for non-insulin-dependent diabetes mellitus (NIDDM) and coronary artery disease (Dahlgren et al., 1992; Ehrmann et al., 1999; Legro et al., 1999; Cibula et al., 2000). Moreover, improvement of skin androgenic symptoms also requires long-term medication. Combined oral contraceptives (COC) remain the first choice for the treatment of hyperandrogenism, as a key endocrine disturbance, for most women with PCOS. COC have been shown to inhibit significantly the ovarian androgens production and to increase serum androgen binding capacity (Falsetti and Galbignani, 1990; Dahlgren et al., 1998; Gjonnaess, 1999). An effect on adrenal steroidogenesis has also been proposed (Wild et al., 1991). In consequence, treatment with COC significantly reduces serum concentrations of both total and free androgens.

PCOS is a heterogeneous syndrome in that it presents with a broad spectrum of clinical manifestations and endocrine or metabolic disturbances. One of the most important factors determining the phenotype of the disease is the presence or absence of obesity. Approximately 50% of women suffering from PCOS are obese (Yen, 1980). Obesity itself negatively influences the synthesis of sex hormone-binding globulin (SHBG), androgen production, and insulin sensitivity (Kurtz et al., 1999; Cibula et al., 1999). The increased concentrations of androgens and more pronounced insulin resistance were demonstrated in obese PCOS women compared with lean patients (Dunaif et al., 1989; Acién et al., 1999; CiamPELLI et al., 1999). The increased concentrations of androgens and insulin stimulate the synthesis of insulin-like growth factor-I (IGF-I) and suppress SHBG and insulin-like growth factor binding protein-1 (IGFBP-1) production in the liver (Buyalos et al., 1995; Morales et al., 1996). As a result, higher amounts of free, non-bound forms of insulin and IGF-I might influence ovarian steroidogenesis in obese PCOS patients.

Other than the documented differences in endocrine and metabolic parameters in obese and lean patients, little is known
about the effect of the treatment of PCOS women with different body mass index (BMI). This is the first study evaluating the effect of COC treatment in obese versus non-obese women. The aim of this study was to compare the effect of COC, containing low-androgenic progestins on clinical androgenic symptoms, on androgen production, and on lipid profiles in two groups of PCOS patients selected on the basis of their BMI.

Materials and methods

Patients

Overall, 46 women with PCOS were enrolled in the study. PCOS was defined as follows: (i) oligomenorrhea (menstrual cycle longer than 35 days) from menarche; (ii) increased concentrations of at least one androgen; and (iii) clinical manifestations of hyperandrogenism (acne, hirsutism, or both). Only lean patients with a BMI <25 kg/m² and obese patients with a BMI >30 kg/m² were selected. All women were aged over 18 years, had not used hormonal therapy or systemic treatment of acne for the preceding 6 months, and were not using any long-term medication. Women presenting with a secondary endocrine disorder, such as non-classic congenital adrenal hyperplasia, hyperprolactinaemia or thyroid dysfunction, those wishing to conceive within the next 6 months, those with contraindications to COC use, or with a blood pressure >140/90 mmHg were excluded from the study. Altogether, three women withdrew from the study (intolerance of COC treatment in one case, personal reasons in one case). A total of 28 lean and 15 obese women completed the study protocol. All participants were studied before and after 6 months of therapy with monophasic low-dose oral contraceptives containing 30–35 µg ethinyl oestradiol in combination with a low-androgenic progestin (norgestimate, desogestrel or gestodene). All women participating in the study gave their informed written consent. The study was approved by the local Ethics Committee.

Clinical examination

The weight and height of all women were taken to calculate the BMI. Waist and hip circumference were measured in the standing position at the levels of the umbilicus and spina iliaca anterior superior to calculate the waist-to-hip ratio (WHR). Blood pressure readings were taken twice in the sitting position after a 10 min rest. Increased body hair was graded using a previously described method (Ferriman and Gallwey, 1961); hirsutism was defined as follows: (i) oligomenorrhea (menstrual cycle longer than 35 days) from menarche; (ii) increased concentrations of at least one androgen; and (iii) clinical manifestations of hyperandrogenism (acne, hirsutism, or both). Only lean patients with a BMI <25 kg/m² and obese patients with a BMI >30 kg/m² were selected. All women were aged over 18 years, had not used hormonal therapy or systemic treatment of acne for the preceding 6 months, and were not using any long-term medication. Women presenting with a secondary endocrine disorder, such as non-classic congenital adrenal hyperplasia, hyperprolactinaemia or thyroid dysfunction, those wishing to conceive within the next 6 months, those with contraindications to COC use, or with a blood pressure >140/90 mmHg were excluded from the study. Altogether, three women withdrew from the study (intolerance of COC treatment in one case, personal reasons in one case). A total of 28 lean and 15 obese women completed the study protocol. All participants were studied before and after 6 months of therapy with monophasic low-dose oral contraceptives containing 30–35 µg ethinyl oestradiol in combination with a low-androgenic progestin (norgestimate, desogestrel or gestodene). All women participating in the study gave their informed written consent. The study was approved by the local Ethics Committee.

Laboratory investigations

Concentrations of LH, FSH, testosterone, androstenedione, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS), SHBG, total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides were evaluated before and after the treatment. The concentrations of LH, FSH and testosterone were determined by chemiluminescent assay using an ACS:180 autoanalyser (Bayer Diagnostics GmbH, Munich, Germany). The concentrations of DHEA, DHEAS and androstenedione were established using radioimmunoassay methods (Immunootech, IOT, Marseille, France). SHBG was determined using immunoradiometric assay (IRMA) kits (Orion, Finland). The value of the free androgen index (FAI) was calculated according to the following formula: FAI = 100 x testosterone (nmol/l)/SHBG (nmol/l). Serum cholesterol and triglycerides were analysed using CHOD-PAP and GPO-PAP-based kits respectively (Oxochromence, Lachema a.s., Brno, Czech Republic). HDL-cholesterol was determined using an immunoinhibition method (HDL-C Direct, Wako Chemicals GmbH, Neuss, Germany). LDL-cholesterol was calculated according to using the Friedewald formula (LDL-cholesterol = total cholesterol – HDL-cholesterol – triglycerides/2.19 nmol/l) (Friedewald et al., 1972).

The reference values for normal concentrations were as follows: testosterone 0.5–2.63 nmol/l, androstenedione 1.57–5.4 nmol/l, DHEA 0.8–10.5 nmol/l, DHEAS 2.4–14.5 µmol/l and SHBG 43.2–96.0 nmol/l.

Statistical analysis

Due to skewed distribution of the data, the sign test and Wilcoxon’s robust paired test were used for the evaluation of intra-individual differences. Student’s t-test after transformation of original variables to minimum skewness and the Mann–Whitney robust test in the non-transformed variables were used for the evaluation of differences between subjects with BMI <25 kg/m² and those with BMI >30 kg/m². For the evaluation of the pre/post-treatment differences in the two groups with different BMI, the sign test and Wilcoxon’s paired test were used.

Results

The two groups did not differ in mean age (23.5 ± 0.925 versus 25.4 ± 1.362 years). Mean BMI and WHR remained stable during the study in obese women (BMI 32.3 ± 0.262; WHR 0.82 ± 0.017) and lean women (BMI 20.3 ± 1.39; WHR 0.65 ± 0.013). Obese women exhibited significantly lower concentrations of SHBG (P < 0.05), and a higher FAI (P < 0.05) (Table I). However, there were no significant differences in lipid profile in the concentrations of androgens, or in the severity of clinical symptoms between lean and obese PCOS women before the treatment.

The significance of changes in monitored parameters during the study in both groups is demonstrated in Table II. In the group of lean women, highly significant changes in circulating concentrations of testosterone (P < 0.001), androstenedione (P < 0.0001), LH (P < 0.001) and SHBG (P < 0.01) were observed. Obese patients showed a less pronounced yet significant increase in SHBG concentrations (P < 0.01), suppression of testosterone production of borderline significance (P < 0.05), and non-significant changes in androstenedione and LH concentrations. The acne score (P < 0.05) and the severity of increased body hair (P = 0.05) were significantly improved in lean women only. The concentration of total cholesterol increased significantly (P < 0.05) during the treatment in both groups; an increase in LDL-cholesterol (P < 0.05) was demonstrated only in lean patients.

Discussion

The BMI exceeds the limit for obesity in about 50% of PCOS patients. An increased BMI impairs many endocrine
and metabolic parameters. First, obesity significantly influences circulating concentrations of SHBG. BMI is inversely correlated with SHBG in healthy women (Glass et al., 1981; Purifoy et al., 1981; Pasquali et al., 1987), as well as in women with PCOS (Dunaif et al., 1987; Graf et al., 1990).

Conflicting results have been reported in terms of a correlation between BMI and androgen production. Significantly increased production rates of androstenedione and DHEA were demonstrated in obese non-PCOS women versus normal-weight women (Kirschner et al., 1983; Kurtz et al., 1987). Higher concentrations of androgens in obese PCOS patients were documented by several authors (Dunaif et al., 1988; Conway et al., 1989), but not confirmed by others (Golland et al., 1990; Graf et al., 1990). Recently, a negative effect of obesity on plasma concentrations of testosterone and SHBG in PCOS patients was reported (Ciampelli et al., 1999). These findings were supported by Acién et al. who found a correlation between BMI and testosterone concentrations (Acién et al., 1999).

Moreover, the presence of obesity has a major impact on the lipid profile and insulin metabolism. PCOS and obesity exert a synergistic deleterious effect on glucose tolerance and insulin sensitivity (Ciampelli et al., 1999). Many studies have demonstrated a more atherogenic lipid profile in obese...
PCOS patients (Falsetti and Pasinetti, 1995). Furthermore, a positive relationship between BMI and plasminogen activator inhibitor-1 (PAI-1) activity and a negative relationship between BMI and IGFBP-1 were found in PCOS women (Morales et al., 1996; Atiomo et al., 2000).

As a result, obesity is one of the main factors determining the phenotype of the disease. There are many pathogenic mechanisms which could adversely influence the treatment of obese PCOS women. However, little is known about the influence of BMI on the effect of different treatment modalities. One exception documented a significantly worsened response by obese PCOS women undergoing ovarian electrocauterity (Gjonnaess, 1994).

This study appears to be the first evaluating a different response by PCOS patients to COC on the basis of their obesity. Oral contraceptives are a therapeutic modality which addresses many of the endocrine disturbances associated with PCOS. The treatment corrects androgen overproduction by several mechanisms, including gonadotrophin suppression, stimulation of the androgen binding capacity, and suppression of ovarian and adrenal androgen synthesis. Reducing the concentrations of free and total androgens during COC treatment of PCOS patients has been demonstrated in many studies (Falsetti and Pasinetti, 1990; Dahlgren et al., 1998; Gjonnaess, 1999).

Agents containing norgestimate, desogestrel, and gestodene were used in the current study. All of the above gestagens are classified into the same group of what is referred to as low-androgenic progestins or ‘new progestins’ (Speroff and DeCherney, 1993; Collins, 1994). The minimal androgenicity of these progestins is reflected in significant increases in SHBG concentrations in users of combined COC (Bergink et al., 1981; Hammond et al., 1984; Palatsi et al., 1984; van der Vange, et al., 1990). A consequence of decreased concentrations of free androgens and minimal affinity of new progestins alone to the androgenic receptor is a beneficial effect of COC on skin androgenic symptoms (Mango et al., 1996; Lucky et al., 1997; Redmond et al., 1997). The low androgenic potency of progestins also influences the effect of COC on the lipid profile. A number of reports showed that COC containing new progestins elevate cholesterol slightly, exert a neutral or positive effect on LDL-cholesterol, and substantially increase concentrations of HDL-cholesterol (Petersen et al., 1988; Gevers Leuven et al., 1990; Kuhl et al., 1990; Falsetti and Pasinetti, 1995). Besides reduction of the LDL-cholesterol/ HDL-cholesterol ratio, a significant elevation of triglycerides has been reported.

The objective of the current study was to evaluate the effect of COC treatment on hyperandrogenism, on clinical androgenic symptoms, and on lipid profile. A limitation of the study was that it did not determine changes in insulin action, which might be an important factor in the pathogenesis of the disease, at least in part of PCOS subjects. In accordance with the literature, significantly lower concentrations of SHBG and lower FAI values were found in the group of obese women. On the other hand, it was not possible to confirm any differences in lipid parameters or in the concentrations of androgens between the two groups. Although no differences were found in androgen production between lean and obese women before treatment, highly significant changes in androgen concentrations were demonstrated in lean women, but only a minor positive effect of the treatment in obese patients. The most marked difference in treatment outcome between the two groups was found in androstenedione, with lean women showing a highly significant decline in serum concentrations whereas circulating concentrations were not significantly altered in obese women. SHBG production likewise was increased in a more pronounced fashion in lean women. The different effect of treatment on androgen production is consistent with a different clinical outcome. The acne score and the grade of increased body hair growth improved significantly only in non-obese subjects.

Surprisingly, no beneficial effect of COC treatment on lipid profile was observed. The slightly increased concentrations of total cholesterol in both groups, like the raised LDL-cholesterol concentrations in lean women, are consistent with published data (Petersen et al., 1988; Kuhl et al., 1990). However, an increase in HDL-cholesterol, reportedly associated with new progestin-containing agents by healthy users and PCOS women alike (Peterson et al., 1988; Gevers Leuven et al., 1990), was not demonstrated in either of the patient groups.

The finding in the current study of an adverse effect of obesity on treatment outcome underlines the need for an individualized approach to long-term treatment of PCOS women. The optimal treatment modality in obese women seems to be weight reduction, where the effect on androgen production and insulin sensitivity has been well demonstrated (Pasquali et al., 1989; Andersen et al., 1995; Holte et al., 1995). However, other possibilities should be considered for the future, such as a combination of COC with insulin-receptor sensitizers. Future studies are warranted to evaluate the efficacy of these combinations in obese women.

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