Low-dose combination of flutamide, metformin and an oral contraceptive for non-obese, young women with polycystic ovary syndrome

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BACKGROUND: The endocrine-metabolic status of non-obese, young women with polycystic ovary syndrome (PCOS) is normalized more effectively by combined treatment with flutamide and metformin than by either of these drugs in monotherapy. In this follow-up study, we assess whether the endocrine-metabolic benefits of combined flutamide-metformin treatment are maintained in the presence of a low-dose oral contraceptive (OC). METHODS: To a population of non-obese, young PCOS women already receiving flutamide-metformin (125 mg/day and 1275 mg/day), a low-dose OC (ethinyl estradiol 20 μg + gestodene 75 μg) was administered to reduce the risk of pregnancy. A total of 12 women elected to receive the OC and this subgroup (OC+) was matched to a subgroup continuing on flutamide-metformin alone (OC−), for a total study population of 24 women (mean age ± SEM 18.7 ± 0.3 years; body mass index, 21.8 ± 0.5 kg/m²). Endocrine-metabolic indices were assessed before any treatment (0 months), on flutamide-metformin (12 months), and again after a further 6 months with or without additional OC (18 months). RESULTS: In OC− and OC+ women, the beneficial effects of flutamide-metformin alone (OC−), for a total study population of 24 women (mean age ± SEM 18.7 ± 0.3 years; body mass index, 21.8 ± 0.5 kg/m²). Endocrine-metabolic indices were assessed before any treatment (0 months), on flutamide-metformin (12 months), and again after a further 6 months with or without additional OC (18 months). RESULTS: In OC− and OC+ women, the beneficial effects of flutamide-metformin on hyperandrogenaemia, hyperinsulinaemia and dyslipidaemia were maintained. In OC+ women, there was an additional increase in sex hormone-binding globulin (SHBG), and thus a further drop in the free androgen index. CONCLUSION: When a low-dose OC is administered with a low-dose flutamide-metformin combination in women with PCOS, the beneficial effects are maintained on hyperinsulinaemia-dyslipidaemia, which are key determinants of long-term complications. Hence, in daily practice, such a low-dose quatuor may become a therapeutic option of first choice for young women with PCOS.

Key words: dyslipidaemia/flutamide/hyperinsulinism/metformin/oral contraception

Introduction

Monotherapies with insulin-sensitizing and anti-androgen agents have been used in the treatment of adolescents and young women with polycystic ovary syndrome (PCOS) (i.e., hyperinsulinism, hyperandrogenism, dyslipidaemia and anovulation) (Nestler and Jakubowicz, 1997; de Leo et al., 1998; Nestler et al., 1998; Ibáñez et al., 2000a,b, 2001; Moghetti et al., 2000; Azziz et al., 2001). These monotherapies are partially effective treatments that act through different pathways and, accordingly, have a different spectrum of endocrine-metabolic actions (Simard et al., 1986; Stumvoll and Häring, 2001).

The endocrine-metabolic status of 31 non-obese, young women with PCOS was recently found to be normalized more effectively by combined treatment with flutamide (250 mg/day) and metformin (1275 mg/day) than by either of these drugs in monotherapy, over 9 months; flutamide-metformin proved particularly effective in correcting dyslipidaemia and hyperandrogenaemia (Ibáñez et al., 2002).

An epi-phenomenon of flutamide-metformin therapy was a striking increment in the ovulation rate, thus pointing to the possible need for concomitant contraception (since flutamide is contra-indicated in pregnancy) and raising the question whether the benefits of the combined flutamide-metformin treatment would be maintained, if an oral contraceptive (OC) were added (Ibáñez et al., 2002).

To answer this question, we report here on the course of the original study cohort (Ibáñez et al., 2002) during the 9 months following a period of 9 months on flutamide and/or metformin treatment, for a total follow-up of 18 months.

Materials and methods

Study population
The original cohort consisted of 31 non-obese, young women (mean age ± SEM: 18.7 ± 0.3 years; range, 18–22) who were 5–10 years beyond menarche and who were using a non-hormonal contraceptive method, if any (Ibáñez et al., 2002).
All women had: (i) hyperinsulinemia on standard 2 h oral glucose tolerance testing (oGTT), defined as peak serum insulin concentration >150 µU/ml (Vidal-Puig and Moller, 1997) and/or mean serum insulin (MSI) >84 mU/l (Ibañez et al., 1997); (ii) ovarian hyperandrogenism, as defined by hirsutism (score ≥8 on Ferriman-Gallwey scale) (Ferriman and Gallwey, 1961), plus elevated serum androstenedione, total testosterone and/or free androgen index [testosterone × 100/sex hormone-binding globulin (SHBG)], an index of free testosterone (Ibañez et al., 1994); and 17-hydroxyprogesterone (17-OHP) hyperresponse (>160 ng/dl) to leuprolide acetate, a GnRH agonist (Procrin, Abbott, Madrid, Spain) (Ibañez et al., 1994); and 17-hydroxyprogesterone (17-OHP) hyperresponse (>160 ng/dl) to leuprolide acetate, a GnRH agonist (Procrin, Abbott, Madrid, Spain) (Ibañez et al., 1994).

None of the women had a body mass index (BMI) >25 kg/m²; thyroid dysfunction; hyperprolactinaemia; abnormal glucose tolerance (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997); a family or personal history of diabetes mellitus; late-onset congenital adrenal hyperplasia (New et al., 1983; Sakkal-Alkadour et al., 1996); evidence of thromboembolic or hepatic disease, or was receiving a medication known to affect gonadal or adrenal function, or carbohydrate- or lipid-metabolism.

Study design
The study protocol is summarized in Figure 1. At the start of the study, women were randomized to receive, once daily, flutamide (Eulexin, Schering-Plough, Spain, 250 mg), metformin (Diaiben, Andreu-Roche, Spain, 1275 mg) or flutamide-metformin (250 mg and 1275 mg) for 9 months (Ibañez et al., 2002). Between months 9–12, all women received flutamide-metformin (Flu-Met), but with a lower flutamide dose (125 mg/day). Between months 12–18, a monophasic, low-dose estro-progestogen OC (ethinyl estradiol 20 µg + gestodene 75 µg; Meliane, Schering) was also taken to avoid pregnancy risk. A total of 12 young women elected to take an OC (OC+), and this subgroup was then matched to a subgroup of 12 women who continued on Flu-Met alone (OC–); clinical and endocrine-metabolic variables were matched, not only at 0 months, but also at 12 months, by which time a considerable normalization of the endocrine-metabolic state had occurred (Tables I and II).

Fasting serum glucose and insulin were assessed at 12 and 18 months, together with LH, FSH, estradiol, testosterone, androstenedione, dehydroepiandrosterone-sulphate (DHEAS), SHBG, and lipid profile. Blood count and liver and kidney function were also screened as additional safety variables.

Hormonal assays
Serum glucose was measured by the glucose oxidase method. Immunoreactive insulin was assayed by IMx (Abbott Diagnostics, Santa Clara, CA, USA). The mean intra- and inter-assay coefficients of variation (CVs) were 4.7 and 7.2% respectively. LH, FSH and progesterone were measured by immuno-chemiluminescence (IMMULITE 2000; Diagnostic Products Corp, Los Angeles, CA, USA), with CVs of 3.5 and 5.0% for LH, 4.6 and 6.3% for FSH, and 7.8 and 8.5% for progesterone. Serum testosterone, 17-OHP, androstenedione, estradiol, SHBG and DHEAS levels were assayed as previously described (Ibañez et al., 2002). Serum samples were kept frozen at −20°C until assay.

Statistics and ethics
Results are expressed as mean ± SEM. Two-sided t-test was used for statistical comparisons, unless mentioned otherwise; significance level was set at P < 0.01.

The study protocol was approved by the Institutional Review Board of Sant Joan de Déu, Barcelona University Hospital. Informed consent was obtained from each woman.
There is a solid pathophysiological basis for considering a low-dose combination of an anti-androgen and an insulin-sensitizer as a therapeutic approach for non-obese women with hyperinsulinemic hyperandrogenism (Ibáñez et al., 2002). However, since an increment of ovulation rate is part of the remarkable efficacy of this combination, the timely addition of contraceptive measures is a major point of attention. The present findings indicate that the main clinical and endocrine-metabolic benefits of a low-dose flutamide-metformin combination are maintained after the addition of a low-dose third-generation estro-progestogen. Another study design would be needed to verify whether, conversely, the addition of flutamide-metformin to a low-dose OC does indeed offer additional endocrine-metabolic benefits, compared with OC alone. It also remains to be studied, in women receiving an OC, to what extent the addition of low-dose flutamide-metformin is metabolically superior to the addition of metformin alone.

Monotherapy with OCs has long been considered the first therapeutic approach in PCOS women who wish to get pregnant. These drugs increase circulating SHBG and suppress adrenal and ovarian androgen production, and thus reduce the clinical markers of androgen excess (Coenen et al., 1996; Venturoli et al., 1999); in addition, their use does not seem to be associated with an increased risk of breast cancer, even when started at a young age (Marchbanks et al., 2002). However, the effects of OCs on PCOS-associated dyslipidaemia and hyperinsulinism are still controversial (Crook et al., 1993; Pedersen et al., 2000; Cibula et al., 2002). For example, a combination of ethinyl estradiol and cyproterone-acetate (2 mg/day), one of the most commonly prescribed regimens for PCOS, is effective in reducing hirsutism (Venturoli et al., 1999), but may facilitate weight gain and decrease both insulin sensitivity and circulating high-density lipoprotein (HDL)-cholesterol (Venturoli et al., 1999; Morin-Papunen et al., 2000; Carmina, 2002); in turn, these adverse effects may be reduced by the addition of metformin (Elter et al., 2002), but the long-term efficacy and safety of such a combination remain to be established.

Combined flutamide-metformin therapy was well-tolerated in both the OC+ and OC− subgroups. The safety and efficacy of metformin in PCOS has been addressed in many populations, including in adolescents and pregnant women (Nestler and Jakubowicz, 1997; Nestler et al., 1998; Ibáñez et al., 2000b, 2001; Moghetti et al., 2000; Glueck et al., 2002, Jakubowicz et al., 2002). The side-effects of flutamide are essentially dose-dependent (Muderris et al., 1997); hepatotoxicity is a potential complication with daily doses >500 mg (Wysowski et al., 1993), this cut-off dose being 4-fold higher than the flutamide dose used in the present study.

In conclusion, when a low-dose OC is added to low-dose flutamide-metformin in women with PCOS, then the beneficial effects are maintained on hyperinsulinaemia and dyslipidaemia, which are the key determinants of the long-term complications of PCOS. Hence, in daily practice, such a low-dose quatuor may become a therapeutic option of first choice for women with PCOS.

### Table II. Clinical and endocrine-metabolic variables, in fasting condition, at study start (0 months) and on flutamide-metformin (Flu-Met; 12 months); thereafter (12–18 months), an oral contraceptive (OC) consisting of a low-dose estro-progestagen was either added to flutamide-metformin (Flu-Met/OC+) or not (Flu-Met/OC−) for 6 months

<table>
<thead>
<tr>
<th></th>
<th>0 monthsa</th>
<th>12 monthsb,c</th>
<th>18 months</th>
<th>Flu-Met (OC−)</th>
<th>Flu-Met (OC+)</th>
<th>Flu-Met/OC−</th>
<th>Flu-Met/OC+</th>
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<tr>
<td></td>
<td>(Flu-Met/OC−)</td>
<td>(Flu-Met/OC+)</td>
<td></td>
<td>Flu-Met (OC−)</td>
<td>Flu-Met (OC+)</td>
<td>Flu-Met/OC−</td>
<td>Flu-Met/OC+</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21.9 ± 0.6</td>
<td>21.8 ± 0.7</td>
<td>22.0 ± 0.6</td>
<td>21.4 ± 0.7</td>
<td>22.0 ± 0.6</td>
<td>21.7 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Ferriman and Gallywey score</td>
<td>16.6 ± 1.3</td>
<td>16.1 ± 1.1</td>
<td>9.3 ± 0.8</td>
<td>8.3 ± 0.6</td>
<td>8.4 ± 0.6</td>
<td>7.6 ± 0.6</td>
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<tr>
<td>Glucose (mmol/l)</td>
<td>4.6 ± 0.1</td>
<td>4.6 ± 0.1</td>
<td>4.6 ± 0.1</td>
<td>4.5 ± 0.1</td>
<td>4.6 ± 1.0</td>
<td>4.7 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>101.2 ± 11.5</td>
<td>86.8 ± 7.9</td>
<td>76.1 ± 4.3</td>
<td>69.6 ± 4.3</td>
<td>71.0 ± 5.0</td>
<td>66.7 ± 6.5</td>
<td></td>
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<tr>
<td>SHBG (nmol/l)</td>
<td>27.8 ± 3.4</td>
<td>27.7 ± 3.2</td>
<td>45.1 ± 3.5</td>
<td>48.6 ± 3.1</td>
<td>45.1 ± 3.3</td>
<td>90.3 ± 6.9c</td>
<td></td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>4.4 ± 0.5</td>
<td>3.5 ± 0.3</td>
<td>2.4 ± 0.1</td>
<td>2.1 ± 0.1</td>
<td>2.4 ± 0.1</td>
<td>2.5 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>Free androgen index</td>
<td>17.6 ± 3.2</td>
<td>12.9 ± 1.6</td>
<td>5.8 ± 0.5</td>
<td>4.8 ± 0.5</td>
<td>5.4 ± 0.5</td>
<td>2.8 ± 0.3c</td>
<td></td>
</tr>
<tr>
<td>Androstenedione (nmol/l)</td>
<td>10.9 ± 1.0</td>
<td>9.6 ± 0.8</td>
<td>7.7 ± 0.4</td>
<td>6.5 ± 0.4</td>
<td>7.4 ± 0.4</td>
<td>7.1 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>DHEAS (nmol/l)</td>
<td>7.5 ± 0.6</td>
<td>6.5 ± 0.5</td>
<td>5.6 ± 0.4</td>
<td>4.5 ± 0.2</td>
<td>5.1 ± 0.3</td>
<td>4.1 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>2.9 ± 0.2</td>
<td>2.8 ± 0.1</td>
<td>2.0 ± 0.1</td>
<td>2.0 ± 0.1</td>
<td>2.0 ± 0.1</td>
<td>2.2 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.4 ± 0.1</td>
<td>1.4 ± 0.1</td>
<td>1.8 ± 0.1c</td>
<td>1.8 ± 0.1c</td>
<td>1.8 ± 0.1</td>
<td>1.8 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>0.7 ± 0.05c</td>
<td>0.7 ± 0.04c</td>
<td>0.6 ± 0.05</td>
<td>0.8 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>Ovulatory:Anovulatory</td>
<td>2:10</td>
<td>1:11</td>
<td>8:4d</td>
<td>9:3d</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

aP < 0.01 between OC− and OC+ subgroups, for all variables.
bP < 0.01 versus OC− subgroups.
cP < 0.01 versus start.
dSEM.

Values are mean ± SEM. P-values by two-sided t-test.

### Discussion

This is a valid input.
Acknowledgements

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References


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