Role of Metformin at the Start and after More than One Year of Therapy

Lourdes Ibáñez and Francis de Zegher


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Flutamide-Metformin plus Ethynylestradiol-Drospirenone for Lipolysis and Antiatherogenesis in Young Women with Ovarian Hyperandrogenism: The Key Role of Metformin at the Start and after More than One Year of Therapy

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Flutamide (Flu)-metformin (Met) with ethynylestradiol-drospirenone is a combination therapy that reduces the total and abdominal fat excess, diminishes the lean mass deficit, and attenuates the dysadipocytokinemia of young and nonobese women with ovarian hyperandrogenism, a variant of polycystic ovary syndrome. We have now questioned the need: 1) to add Met at the start of Flu plus ethynylestradiol-drospirenone; and 2) to maintain Met after more than 1 yr on full combination therapy.

The additive effects of Met (850 mg/d) were assessed in studies A and B, over 3 months, in young patients with hyperinsulinemic hyperandrogenism. In study A, all participants (n = 31; age = 16 yr; body mass index = 22 kg/m²) started on Flu (62.5 mg/d) and an oral contraceptive (ethinyl-estradiol + drospirenone), and they were randomized to receive Met in addition or not. In study B, all participants (n = 42; age = 19 yr; body mass index = 22 kg/m²) had been treated with Flu-Met plus the same contraceptive for a mean duration of 17 months, and they were randomized for discontinuation of Met or not.

In conclusion, Met proved to be a pivotal component of a prime combination therapy that attenuates the dysadipocytokinemia, the lean mass deficit, and the central adiposity of young patients with polycystic ovary syndrome. (J Clin Endocrinol Metab 90: 39–43, 2005)

POLYCYSTIC OVARY SYNDROME (PCOS), a variable constellation of anovulatory hyperandrogenism with hyperinsulinemia and/or dyslipidemia, is the most frequent endocrine disorder of young women (1–3). One of the physical stigmas of women with PCOS, even if nonobese, is an excess of central fat and a deficit of lean mass, both of which seem to be reflections of the prolonged dysadipocytokinemia that accompanies hyperinsulinemic hyperandrogenism and that is aggravated by monotherapy with an oral estrogenestrogen contraceptive (OC) even with an OC containing drospirenone (4–8).

At present, there is no approved therapy for PCOS. Low-dose flutamide (Flu)-metformin (Met) plus ethynylestradiol-drospirenone was recently found to reduce total and abdominal fat excess, to diminish the deficit in lean mass, and to attenuate the dysadipocytokinemia (as judged by IL-6 and adiponectin) in young and nonobese women with PCOS (8–10). The development of this combination therapy departed from the evidence that Flu and Met exert additively beneficial effects on endocrine-metabolic indices (11) and that, together, they are capable of correcting the dysadipocytokinemia and the adiposity of young PCOS patients (5, 6, 8, 9).

In two randomized pilot studies (A and B), we assessed the additive effects of Met in young PCOS patients (A) at the start of Flu and a drospirenone-containing OC, and (B) after more than 1 yr on Flu-Met plus the same OC.

Subjects and Methods

Study population

Study A. The population consisted of 31 young patients with PCOS [mean ± sem; age, 16.0 ± 0.3 yr; range, 13–20 yr; body mass index (BMI), 22.2 ± 0.4 kg/m²; range, 17.4–25.9 kg/m²; 2–6 yr post menarche].

Inclusion criteria were: 1) hyperinsulinemia on a standard 2-h oral glucose tolerance test, defined as peak serum insulin levels more than 150 mU/liter and/or mean serum insulin more than 84 μU/ml; and 2) ovarian hyperandrogenism as defined by hirsutism (Ferriman-
Gallwey score above 8); and high serum androstenedione, total testo-
sterone, or free androgen index (testosterone × 100/SHBG); and a
17-hydroxyprogesterone hyperresponse (>160 ng/dl) to GnRH ag-
onist (leuprolide acetate, Procrin, Abbott, Madrid, Spain, 500 µg sc).
Before study start, none of the patients were receiving a contraceptive
or another medication known to affect gonadal or adrenal function, or
carbohydrate or lipid metabolism.

Study B. The population consisted of 42 PCOS patients (age, 19.3 ± 0.4
yr; range, 16–23 yr; BMI, 21.7 ± 0.4 kg/m²; range, 15.4–27.5 kg/m²; 5–13
yr post menarche).

All patients had been diagnosed with hyperinsulinemic ovarian hy-
perandrogenism according to the criteria of Study A, and they had been
interventional treatment with Met (850 mg/d) plus a monophasic OC
(Yasmin, Schering, Madrid, Spain; ethinylestradiol 30 µg) + drospirenone (3 mg), 21 d/month), for an average duration of 17
months (range, 15–21 months). Studies A and B. Exclusion criteria were: a BMI ≥ 26 kg/m²; evidence of thyroid dysfunction, Cushing’s syndrome, hyperprolactinemia; glucose
intolerance (17); family or personal history of diabetes mellitus; late-
onset congenital adrenal hyperplasia (18, 19); abnormal blood count or
serum electrolytes; abnormal screening results for liver and kidney
function.

The studies were conducted in Barcelona, after approval by the
Institutional Review Board of Sant Joan University Hospital; in-
formed consent was obtained from the patients and/or their parents,
with assent from minors. None of the results in the present studies
have been reported previously.

Study design

Both studies were open labeled; treatment subgroups were assembled
by randomization (1:1 ratio; Gran Mos program, Medical Research
Institute of Barcelona) (5, 8, 9).

**TABLE 1.** Clinical, hormonal, cytokine, and dual-energy x-ray absorptiometry variables in adolescents (n = 31; mean age 16 yr; height
160 cm; 2–6 yr post menarche) with hyperinsulinemic hyperandrogenism, who were randomized to receive treatment with Flu (62.5 mg/d)
and an OC [OC and Flu (+) Met (-); n = 15] or to receive, in addition, Met [OC and Flu (+) Met (+); n = 16] for 3 months

<table>
<thead>
<tr>
<th></th>
<th>OC and Flu (+) Met (-)†</th>
<th>OC and Flu (+) Met (+)†</th>
<th>Change over 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 month</td>
<td>3 months</td>
<td>0 month</td>
</tr>
<tr>
<td><strong>Lean mass (kg)</strong></td>
<td>35.3 ± 0.9</td>
<td>35.2 ± 0.8</td>
<td>34.4 ± 1.0</td>
</tr>
<tr>
<td><strong>Fat mass (kg)</strong></td>
<td>19.4 ± 2.2</td>
<td>19.8 ± 2.3</td>
<td>21.7 ± 1.8</td>
</tr>
<tr>
<td><strong>Total fat mass (kg)</strong></td>
<td>36.7 ± 2.8</td>
<td>37.0 ± 2.6</td>
<td>36.1 ± 2.5</td>
</tr>
<tr>
<td><strong>Abdominal fat mass (kg)</strong></td>
<td>18.2 ± 3.1</td>
<td>18.6 ± 3.2</td>
<td>18.0 ± 3.0</td>
</tr>
<tr>
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<td>18.0 ± 3.0</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. To convert units to SI, multiply the concentrations of testosterone by 0.03467, those of androstenedione by 0.0349,
those of DHEAS by 0.02714; and divide the concentrations of SHBG by 0.0288, those of triglycerides by 88.5, and those of HDL cholesterol and
LDL cholesterol by 38.7.

† No significant differences between randomized subgroups at 0 month.

*Glucose, mg/dl; insulin, mU/L.

*P ≤ 0.01 and †P ≤ 0.001 vs. 0 month.

*P ≤ 0.01 and †P ≤ 0.001 for 0- to 3-month change vs. the Met (-) subgroup.

**Fig. 1.** Changes over 3 months in lean body mass, body fat mass, and abdominal fat mass in 31 young patients (age -16 yr) with hyperinsulinemic ovarian hyperandrogenism. All participants started on Flu and an OC [ethinylestradiol (EE) + drospirenone], and they were randomized to receive Met (850 mg/d) in addition (●, Met +, n = 16) or not (○, Met −, n = 15). The addition of Met was found to increase lean
mass and to reduce total and abdominal fat excess, without changing body weight (see Table 1 for values).
Study A
All participants started at month zero on Flu (62.5 mg/d) and a monophasic OC (Yasmin) and were randomized to receive Met addition [850 mg, once daily at dinner time, for 3 months; OC and Flu (H11001/H11002); n = 5.1% (8, 9)]. Adiponectin was measured by RIA (Linco Research, St. Charles, MO); intra- and interassay CVs were 6.2% and 6.9% (8, 9). Samples were stored at -20°C until assay.

For uniformity, results are expressed as mean ± SEM. Two-sided t tests (paired or unpaired, as appropriate) were used for statistical comparisons between subgroups; per variable, only one comparison was performed; significance level was set at P < 0.05.

Results

Study A
Table 1 and Fig. 1 summarize the main findings. At the start, the study population was characterized by hyperandrogenism, dysadipocytokiniemia, and central adiposity; five of 31 patients had regular menses (cycles of 25–35 d), and 26 were oligo- or amenorrheic. Patients receiving Flu plus OC experienced decreases in testosterone, androstenedione, DHEAS, and low-density lipoprotein (LDL) cholesterol, as well as increments in SHBG, adiponectin, and high-density lipoprotein (HDL) cholesterol, irrespective of whether Met was added. By comparison of 3-mo changes between subgroups, however, the addition of Met was found to have consistently beneficial effects on IL-6 and body adiposity, whereas body weight remained unchanged. Two adolescents experienced spotting without breakthrough bleeding at the beginning of the first or second cycle on OC. Each treatment was well tolerated; indices of hepatic and renal function remained unchanged.

Study B
Table 2 summarizes the main findings. After more than 1 yr on Flu-Met plus OC, changes were still ongoing (SHBG, DHEAS, adiponectin, lean mass). Comparison of 3-mo changes between subgroups disclosed that maintenance of Met addition still had detectably beneficial effects on circulating IL-6 and adiponectin, as well as on body adiposity.

**TABLE 2.** Clinical, hormonal, cytokine, and dual-energy x-ray absorptiometry variables in young women (n = 42; age ≈19 yr; height 159 cm; 5–13 yr post menarche) with hyperinsulinemic hyperandrogenism, who had been treated with Flu (62.5 mg/d) and Met (850 mg/d) together with an OC for an average of 17 months and who were randomized to discontinue Met [OC and Flu (+) Met (-); n = 20] or not [OC and Flu (+) Met (+); n = 22] for the subsequent 3 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>OC and Flu (+) Met (-)</th>
<th>OC and Flu (+) Met (+)</th>
<th>Change over 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 month</td>
<td>3 months</td>
<td>0 month</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.0 ± 0.6</td>
<td>22.1 ± 0.6</td>
<td>21.4 ± 0.5</td>
</tr>
<tr>
<td>Fasting glucose/insulin ratio *</td>
<td>8.3 ± 0.8</td>
<td>8.7 ± 0.9</td>
<td>10.1 ± 0.8</td>
</tr>
<tr>
<td>SHBG (µg/dl)</td>
<td>3.7 ± 0.3</td>
<td>4.5 ± 0.3</td>
<td>4.1 ± 0.3</td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>59 ± 6</td>
<td>57 ± 6</td>
<td>67 ± 8</td>
</tr>
<tr>
<td>Androstenedione (ng/dl)</td>
<td>217 ± 18</td>
<td>215 ± 17</td>
<td>189 ± 13</td>
</tr>
<tr>
<td>DHEAS (µg/dl)</td>
<td>188 ± 17</td>
<td>182 ± 16</td>
<td>178 ± 16</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>95 ± 6</td>
<td>97 ± 5</td>
<td>91 ± 6</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>73 ± 4</td>
<td>78 ± 4</td>
<td>74 ± 2</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>86 ± 8</td>
<td>84 ± 7</td>
<td>89 ± 9</td>
</tr>
<tr>
<td>IL-6 (fg/ml)</td>
<td>757 ± 65</td>
<td>834 ± 61</td>
<td>880 ± 117</td>
</tr>
<tr>
<td>Adiponectin (µg/ml)</td>
<td>10.7 ± 0.7</td>
<td>10.0 ± 0.6*</td>
<td>9.5 ± 0.5</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>20.7 ± 1.3</td>
<td>20.9 ± 1.4</td>
<td>17.5 ± 1.2</td>
</tr>
<tr>
<td>Abdominal fat mass (kg)</td>
<td>4.9 ± 0.4</td>
<td>5.1 ± 0.4*</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>Lean mass (kg)</td>
<td>33.6 ± 1.0</td>
<td>33.5 ± 1.0</td>
<td>34.6 ± 1.1</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. To convert units to SI, multiply the concentrations of testosterone by 0.03467, those of androstenedione by 0.03499, those of DHEAS by 0.02714; and divide the concentrations of SHBG by 0.02888, those of triglycerides by 88.5, and those of HDL cholesterol and LDL cholesterol by 38.7.

* No significant differences between randomized subgroups at 0 month.

f Glucose, mg/dl; insulin, mU/liter.

& P < 0.05; & P ≤ 0.01; and & P ≤ 0.001 vs. 0 month.

h P < 0.05; h P ≤ 0.01; and (after log-transformation) h P ≤ 0.001 for 0- to 3-month change vs. the Met (-) subgroup.
Treatments were well tolerated; indices of hepatic and renal function remained stable.

Discussion

In a young PCOS population, we compared the efficacy of Flu plus ethinylestradiol-drospirenone to that of the same duo plus Met. Efficacy was not only judged by classic markers such as BMI, fasting glucose/insulin and lipids, testosterone, and SHBG, but also by indices related to atherogenesis, such as proinflammatory IL-6, antiinflammatory adiponectin, and central adiposity (8, 9, 23–27). The compared therapies were found to yield similar results for the classic markers but different or opposite outcomes for the new indices, including for lean mass and for abdominal fat excess; each of the latter outcomes was to the advantage of adding Met. The use of indices such as adipocytokines and body adiposity thus allowed us to unmask the fact that the addition of Met to Flu-OC therapy confers lipolytic and possibly antiatherogenic benefits. These findings corroborate Met as an adjuvant in the long-term prevention of the cardiovascular and metabolic disorders that are linked to PCOS (28–30).

When given in monotherapy to nonobese adolescents or young women with PCOS, Met lowers high testosterone levels, attenuates the low-grade inflammatory state (as judged by circulating C-reactive protein, IL-6, and/or adiponectin), and reduces central adiposity; in monotherapy, Met remains effective for at least 1 yr, and its discontinuation elicits a rapid return to pretreatment conditions (31–33). When given together with Flu, Met is also known to be effective for at least 9 months; discontinuation of such dual therapy is also followed by a swift reversal of treatment benefits (5, 8). When given together with both Flu and a drospirenone-containing OC, Met now proved to still have detectably lipolytic and possibly antiatherogenic effects both at the start and after more than 1 yr of such a triple therapy. In conclusion, Met proved to be a pivotal component of a prime combination therapy that attenuates the dysadipocytokinenia, the lean mass deficit, and the central adiposity of PCOS.

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