

Ethinylestradiol-Drospirenone, Flutamide-Metformin, or Both for Adolescents and Women with Hyperinsulinemic Hyperandrogenism: Opposite Effects on Adipocytokines and Body Adiposity

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Hyperinsulinemic hyperandrogenism with anovulation, the so-called polycystic ovary syndrome (PCOS), is the most frequent endocrine disorder of young women. One of the stigmata of PCOS is a deficit of lean mass and an excess of fat, in particular, abdominal fat, even in the absence of obesity. Adiponectin and IL-6 are among the adipocytokines that have recently been related to abdominal fat excess, insulin resistance states, and cardiovascular disease risk. We studied the effects of two new treatment options, ethinylestradiol-drospirenone and flutamide-metformin, and of their combination on adipocytokines and body adiposity in adolescents and women with PCOS.

Adolescents with PCOS ($n = 32$; age, ~ 15 yr; body mass index, ~ 22 kg/m²) were randomly assigned to receive the oral contraceptive (OC) ethinylestradiol-drospirenone, or the low-dose generic duo of flutamide (62.5 mg/d) plus metformin (850 mg/d). Young women with PCOS ($n = 22$; age, ~ 19 yr; body mass index, ~ 22 kg/m²) were randomized to receive the same OC, either alone or with flutamide-metformin. Fasting blood glucose, serum insulin, lipids, androgens, IL-6, adiponectin, and body composition (by absorptiometry) were assessed at the start, and after 3 and/or 9 months.

At the start, serum concentrations of the proinflammatory IL-6 were high, and those of the antiinflammatory adiponectin were low; body composition was adipose in each subpopulation. Abnormal adipocytokine levels, hypertriglyceridemia,

and body adiposity diverged further from the norm in adolescents on OC; in contrast, girls on flutamide-metformin reverted all study indices toward normal, lost part of their fat excess, and reduced their lean mass deficit. In comparison to the girls on OC, those on flutamide-metformin lost a mean of approximately 4 kg of fat and gained approximately 4 kg of lean mass. Similarly, abnormal adipocytokine levels and adiposity were aggravated in women on OC alone and improved in women on OC plus flutamide-metformin; within 9 months, the latter subgroup lost a mean of approximately 3 kg of fat and gained approximately 3 kg of lean mass, in comparison to women on OC alone.

In conclusion, young and nonobese PCOS patients were found to be in a low-grade, chronic inflammation state, and to have a body adiposity that evolves according to the balance of circulating adipocytokines and lipids, rather than to androgen excess or fasting hyperinsulinemia. Monotherapy with ethinylestradiol-drospirenone may not be a prime choice for PCOS, given its inefficacy to attenuate abnormal adipocytokine levels and body adiposity; ethinylestradiol-drospirenone plus flutamide-metformin, however, is a first OC combination that was found capable of reverting both the adipocytokine balance and the body composition toward normal, and that may therefore improve the long-term cardiovascular perspectives of women with PCOS. (*J Clin Endocrinol Metab* 89: 1592–1597, 2004)

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 stigmata of PCOS is a deficit of lean mass and an excess of fat, in particular, abdominal fat, even in the absence of obesity (4–6). Adiponectin and IL-6 are among the adipocytokines that have been related to abdominal fat excess and/or impaired insulin sensitivity (7–9), suggesting that these cytokines, together with other indices of chronic low-grade inflammation, contribute to the link between insulin resistance states and cardiovascular disease risks (10).

Abbreviations: BMI, Body mass index; CV, coefficient of variation; CRP, C-reactive protein; DXA, dual-energy x-ray absorptiometry; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OC, oral contraceptive; PCOS, polycystic ovary syndrome.

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A first step in traditional treatment for PCOS is to give a second- or third-generation oral contraceptive (OC), even to young teenagers (2); however, such OCs fail to correct the endocrine-metabolic anomalies and the excess of fat (6). Recently, two alternative options have been developed independently, and their combination may be complementary.

The first alternative is to give a fourth-generation OC that contains ethinylestradiol together with a novel progestin, called drospirenone, which is claimed to have properties closer to those of natural progesterone, including antiminerocorticoid and antiandrogenic activities (11, 12). The introduction of this novel OC into clinical practice has been unprecedentedly swift, but its effects in adolescents and young women with PCOS are unknown.

The second alternative is to give an insulin-sensitizing compound, such as metformin (13–17), together with an androgen-receptor blocker, as flutamide (which is contraindicated in pregnancy) (18–20). So far, such dual treatment seems the most effective strategy to improve the endocrine-

metabolic state (21) and the adiposity of PCOS, including the reduction of abdominal fat (4, 5); an increment in ovulation rate is also part of the efficacy, but this epiphenomenon implies a pregnancy risk (5, 21). Therefore, a third-generation OC has been added to this duo, but this addition was found to preclude the loss of abdominal fat (6).

Obese women with PCOS are known to have high serum concentrations of C-reactive protein (CRP), a marker of inflammation and a cardiovascular risk factor; metformin in monotherapy reduces those high CRP levels, whereas combined treatment with ethinylestradiol and cyproterone-acetate raises CRP further (22).

In adolescents with PCOS, we compared the effects of ethinylestradiol-drospirenone to those of low-dose flutamide-metformin, in particular on adiposity and on circulating IL-6 and adiponectin; in young women with PCOS, we compared the effects of ethinylestradiol-drospirenone alone to those of ethinylestradiol-drospirenone plus flutamide-metformin.

Subjects and Methods

Study population and ethics

Fifty-four nonobese adolescents and young women were included in two studies. Adolescent girls who were not at risk of pregnancy (no intercourse) were enrolled in one study and randomized to receive OC or not (OC±); young women at risk of pregnancy were enrolled in the other study (OC+). The OC± population consisted of 32 teenagers (age, 14.6 ± 0.3 yr; range, 13–16 yr; 2–4 yr postmenarche); the OC+ group consisted of 22 young women (age, 18.6 ± 0.3 yr; range, 17–21 yr; 4–8 yr postmenarche).

Inclusion criteria were: 1) hyperinsulinemia on a standard 2-h oral glucose tolerance test, defined as peak serum insulin levels more than 150 μU/ml and/or mean serum insulin more than 84 μU/ml (23, 24); 2) ovarian hyperandrogenism as defined by amenorrhea (absence of menses for > 3 months) or oligomenorrhea (intermenstrual phase > 45 d) and/or hirsutism (Ferriman-Gallwey score > 8) (25); and 3) elevated serum androstenedione and/or testosterone, and excessive 17-hydroxyprogesterone response (>160 ng/dl) to GnRH agonist (leuprolide acetate, 500 μg sc; Abbott Laboratories, Madrid, Spain) (26).

Exclusion criteria were: body mass index (BMI) greater than 25 kg/m²; evidence of thyroid dysfunction, Cushing syndrome, or hyperprolactinemia; glucose intolerance (27); family or personal history of diabetes mellitus; late-onset congenital adrenal hyperplasia (28, 29); use of medication known to affect gonadal or adrenal function or carbohydrate-lipid metabolism; abnormal blood count or serum electrolytes; and abnormal results in screening tests for liver and kidney function.

The study was conducted in Barcelona, Spain, without support from the pharmaceutical industry, after approval by the Institutional Review Board of Sant Joan University Hospital, and after informed consent from parents and/or young women, and assent from minors. None of the subjects or results in the present study have been reported previously.

Study design

The OC± and OC+ studies were open-labeled and had identical designs. In the OC± study, girls were randomized (Grand Moss program) either to receive two tablets, flutamide (62.5 mg) and metformin (850 mg), once daily at dinner without the addition of OC [Flu-Met (+) OC (-); n = 16]; or to receive a monophasic OC (Yasmin, Schering, Madrid, Spain); ethinylestradiol 30 μg + drospirenone 0.3 mg, 21 d/month) without addition of flutamide-metformin [Flu-Met (-) OC (+); n = 16] for 9 months.

In the OC+ study, all participants started on OC (Yasmin), and they were randomized to receive this OC either in monotherapy [OC (+) Flu-Met (-); n = 11] or together with flutamide-metformin in the same low-dose [OC (+) Flu-Met (+); n = 11].

Endocrine-metabolic assessment

Fasting blood glucose, serum insulin, lipid profile, SHBG, and testosterone were determined at baseline and after 3 and 9 months, together with indices of hepatic and renal function, as safety variables; results after 3 months will not be highlighted, as they were intermediate between those at the start and after 9 months for all variables. Serum adiponectin and IL-6 were only measured at study start and after 3 months.

Baseline assessments were performed in the follicular phase (d 3–7) or after 2 months of amenorrhea, and hormonal levels were compared with local references for postmenarcheal females of similar age (5); in addition, 26 postmenarcheal adolescents and young women served as controls for serum adiponectin and IL-6 measurements.

Body composition, assays, and statistics

Body composition was assessed by dual-energy x-ray absorptiometry (DXA) at the start of the study and after 3 and 9 months, with a Lunar Prodigy (Lunar Corp., Madison, WI) coupled to Lunar software (version 3.4/3.5) (30). Absolute (kilograms) whole body fat mass and lean body mass were assessed, as well as fat content in the abdominal region, which was defined as the area between the dome of the diaphragm (cephalad limit) and the top of the great trochanter (caudal limit) (31). Total irradiation dose per assessment was 0.1 mSievert. Coefficients of variation (CVs) for scanning precision were 2.0 and 2.6% for fat and lean body mass, respectively (32); intraindividual CV for abdominal fat mass was 0.7%. Body composition results after 3 months were intermediate between those at the start and after 9 months and will therefore not be highlighted. Body composition references were obtained from healthy volunteers matched for gender, age, height, BMI, and ethnic background.

Serum glucose was measured by the glucose oxidase method. Immunoreactive insulin was assayed by IMX (Abbott, Santa Clara, CA); intra- and interassay CVs were 4.7 and 7.2%, respectively. Serum testosterone, 17-hydroxyprogesterone, and SHBG were assayed as described (15). IL-6 was measured by immunochemiluminescence (IMMULITE 2000, Diagnostic Products Corp., Los Angeles, CA), with a lower detection limit of 100 fg/ml. The intra- and interassay CVs were 3.5 and 5.1%, respectively. Adiponectin was measured by RIA (Linco Research Inc., St. Charles, MO); the intra- and interassay CVs were 6.2 and 6.9%, respectively. Samples were stored at -20 C until assay. For uniformity, results are expressed as mean ± SEM. Two-sided *t* tests were used for statistical comparisons between groups; per variable, only one comparison was performed; significance level was set at *P* < 0.05.

Results

Tables 1 and 2 and Fig. 1 summarize the main findings. At the start (0 months), all study variables were comparable between randomized subgroups. Each treatment was well tolerated; indices of hepatic and renal function remained unchanged.

OC vs. flutamide-metformin in PCOS teenagers (Table 1)

In teenagers receiving OC, there were appreciable decreases in hirsutism score and testosterone, as well as increments in SHBG and high-density lipoprotein (HDL) cholesterol; however, serum triglycerides and body adiposity diverged further from the norm. At the start, IL-6 concentrations were high and adiponectin levels were low, and these indices failed to improve after 3 months on OC. Two adolescents experienced spotting without breakthrough bleeding between the first and second menses on OC.

In girls receiving flutamide-metformin, all abnormal indices reverted toward normal, including testosterone, triglycerides, low-density lipoprotein (LDL) and HDL cholesterol, IL-6, adiponectin, total fat, abdominal fat, and lean

TABLE 1. Clinical, hormonal, cytokine, and DXA variables in adolescent girls (n = 32; mean age, 14.6 yr; height, 161 cm; 2–4 yr postmenarche) with hyperinsulinemic hyperandrogenism, who were randomized to receive either combined treatment with flutamide (62.5 mg/d) and metformin (850 mg/d) without OC [Flu-Met (+) OC (-); n = 16] or ethinylestradiol-drospirenone OC alone [Flu-Met (-) OC (+); n = 16] for 9 months

	Reference ^a	Total	Flu-Met (-) OC (+)			Flu-Met (+) OC (-)		
			0 months	9 months	Δ 0–9 months	0 months	9 months	Δ 0–9 months
BMI (kg/m ²)	21.5 ± 0.5	21.9 ± 0.4	22.0 ± 0.6	22.5 ± 0.5	0.6 ± 0.2	21.8 ± 0.5	22.0 ± 0.6	0.1 ± 0.3
Ferriman and Gallwey score	<8	15.2 ± 0.9	15.1 ± 1.2	10.9 ± 0.7 ⁱ	-4.1 ± 0.7	15.3 ± 1.4	10.4 ± 0.9 ^j	-4.9 ± 0.6
Fasting glucose/insulin ratio ^b	9.8 ± 0.4	7.8 ± 0.4 ^e	8.0 ± 0.6	7.6 ± 0.8	-0.3 ± 0.1	7.7 ± 0.7	10.0 ± 1.5	2.3 ± 1.5
SHBG (μg/dl)	1.9 ± 0.1	0.9 ± 0.1 ^f	1.0 ± 0.1	4.5 ± 0.4 ⁱ	3.5 ± 0.4	1.0 ± 0.1	1.1 ± 0.1 ^g	0.1 ± 0.1 ^k
Testosterone (ng/dl)	31 ± 3	107 ± 9 ^f	107 ± 14	66 ± 10 ^h	-41 ± 13	108 ± 12	61 ± 5 ⁱ	-40 ± 7
Triglycerides (mg/dl)	61 ± 4	79 ± 9 ^e	77 ± 4	97 ± 8 ^g	20 ± 9	81 ± 5	53 ± 4 ⁱ	-29 ± 6 ^k
HDL cholesterol (mg/dl)	62 ± 5	54 ± 1 ^e	54 ± 2	75 ± 4 ⁱ	21 ± 3	53 ± 2	66 ± 2 ⁱ	13 ± 2
LDL cholesterol (mg/dl)	70 ± 5	103 ± 4 ^f	104 ± 6	101 ± 7	-4 ± 8	102 ± 4	75 ± 5 ⁱ	-27 ± 6 ^j
IL-6 ^c (fg/ml)	637 ± 32	901 ± 82 ^e	781 ± 106	1146 ± 203 ^g	365 ± 173	1021 ± 120	638 ± 54 ⁱ	-383 ± 86 ^k
Adiponectin ^c (μg/ml)	12.7 ± 0.8	10.7 ± 0.7 ^d	10.8 ± 1.0	9.9 ± 1.0 ^g	-0.9 ± 0.4	10.7 ± 1.0	13.1 ± 1.2 ^h	2.5 ± 0.7 ^k
Fat mass (kg)	13.6 ± 1.6	19.6 ± 1.0 ^e	19.5 ± 1.4	21.9 ± 1.2 ^h	2.4 ± 0.6	19.7 ± 1.5	17.9 ± 1.6 ⁱ	-1.8 ± 0.4 ^k
Abdominal fat mass (kg)	2.6 ± 0.4	5.7 ± 0.4 ^f	5.3 ± 0.5	5.8 ± 0.5 ^h	0.6 ± 0.2	6.1 ± 0.5	4.6 ± 0.6 ⁱ	-1.5 ± 0.2 ^k
Lean mass (kg)	38.7 ± 1.4	35.5 ± 0.7 ^e	35.9 ± 0.8	34.2 ± 0.8 ^h	-1.7 ± 0.4	35.1 ± 1.2	37.1 ± 1.3 ^h	2.0 ± 0.5 ^k

Values are mean ± SEM.

^a Healthy volunteers matched for height and weight (n = 24 for endocrine-metabolic variables; n = 19 for body composition; age, 15.4 ± 0.1 yr).

^b Glucose, mg/dl; insulin, mU/liter

^c Values at start and after 3 (not 9 months; see *Subjects and Methods*).

^d P < 0.05; ^e P ≤ 0.01; and ^f P ≤ 0.0001 vs. reference.

^g P < 0.05; ^h P ≤ 0.01; and ⁱ P ≤ 0.0001 vs. baseline.

^j P < 0.05; ^k P < 0.001 for 0–9 months changes (Δ) between subgroups.

TABLE 2. Clinical, hormonal, cytokine, and DXA variables in young women (n = 22; mean age, 18.6 yr; height, 162 cm; 4–8 yr postmenarche) with hyperinsulinemic hyperandrogenism, who were randomized to receive treatment with flutamide (62.5 mg/d) and metformin (850 mg/d) with an OC [OC (+) Flu-Met (+); n = 11] or to receive this ethinylestradiol-drospirenone OC alone [OC (+) Flu-Met (-); n = 11] for 9 months

	Reference ^a	Total	Flu-Met (-) OC (+)			Flu-Met (+) OC (+)		
			0 months	9 months	Δ 0–9 months	0 months	9 months	Δ 0–9 months
BMI (kg/m ²)	21.5 ± 0.5	21.7 ± 0.4	21.8 ± 0.7	22.1 ± 0.8	0.3 ± 0.4	21.7 ± 0.6	21.8 ± 0.5	0.1 ± 0.3
Ferriman and Gallwey score	<8	14.0 ± 0.9	13.7 ± 1.0	10.3 ± 0.7 ^h	-3.5 ± 0.5	14.4 ± 2.0	9.3 ± 0.7 ^h	-5.1 ± 0.8
Fasting glucose/insulin ratio ^b	9.8 ± 0.4	7.3 ± 0.5 ^e	6.7 ± 0.6	7.4 ± 0.7	0.7 ± 0.9	8.0 ± 1.8	8.3 ± 0.4	0.4 ± 1.0
SHBG (μg/dl)	1.9 ± 0.1	0.9 ± 0.1 ^e	1.0 ± 0.1	4.0 ± 0.4 ^h	3.0 ± 0.4	0.9 ± 0.1	5.1 ± 0.3 ^h	4.2 ± 0.3 ⁱ
Testosterone (ng/dl)	31 ± 3	105 ± 8 ^e	101 ± 12	60 ± 5 ^g	-41 ± 12	110 ± 11	61 ± 8 ^g	-49 ± 11
Triglycerides (mg/dl)	61 ± 4	89 ± 9 ^e	95 ± 18	115 ± 17 ^f	19 ± 8	83 ± 4	107 ± 11 ^f	24 ± 10
HDL cholesterol (mg/dl)	62 ± 5	52 ± 1 ^d	50 ± 1	77 ± 4 ^h	27 ± 4	55 ± 2	77 ± 5 ^h	22 ± 4
LDL cholesterol (mg/dl)	70 ± 5	109 ± 4 ^e	107 ± 6	100 ± 6	-7 ± 7	111 ± 5	93 ± 7 ^f	-18 ± 6 ⁱ
IL-6 ^c (fg/ml)	637 ± 32	919 ± 61 ^e	954 ± 85	1093 ± 103	139 ± 64	885 ± 91	712 ± 60	-173 ± 93 ^j
Adiponectin ^c (μg/ml)	12.7 ± 0.8	7.9 ± 0.5 ^e	7.7 ± 0.5	7.0 ± 0.5	-0.8 ± 0.4	8.0 ± 0.8	8.8 ± 0.8 ^g	0.8 ± 0.3 ^j
Fat mass (kg)	14.9 ± 1.8	20.6 ± 1.2 ^d	20.1 ± 1.9	21.3 ± 1.9 ^f	1.2 ± 0.5	21.1 ± 1.5	19.6 ± 1.3 ^g	-1.5 ± 0.5 ^k
Abdominal fat mass (kg)	3.0 ± 0.4	6.1 ± 0.6 ^e	6.5 ± 1.0	6.8 ± 1.1 ^f	0.3 ± 0.1	5.6 ± 0.5	4.5 ± 0.5 ^h	-1.1 ± 0.1 ^k
Lean mass (kg)	38.9 ± 1.1	34.5 ± 0.8 ^e	33.9 ± 1.2	32.7 ± 1.2 ^f	-1.2 ± 0.5	35.2 ± 0.9	37.4 ± 0.8 ^h	2.1 ± 0.4 ^k

Values are mean ± SEM.

^a Healthy volunteers matched for height and weight (n = 24 for endocrine-metabolic variables; n = 19 for body composition; age, 15.4 ± 0.1 yr).

^b Glucose, mg/dl; insulin, mU/liter.

^c Values at start and after 3 months (not 9 months; see *Subjects and Methods*).

^d P ≤ 0.01; ^e P ≤ 0.0001 vs. reference.

^f P < 0.05; ^g P ≤ 0.01; and ^h P ≤ 0.0001 vs. baseline.

ⁱ P < 0.05; ^j P ≤ 0.01; ^k P ≤ 0.001 for 0–9 months changes (Δ) between subgroups.

mass. At the start, 12 of 16 girls were oligomenorrheic or amenorrheic, and four had regular menses (cycles of 25–35 d); after 3 months, the menstrual pattern was normal in all.

Over 9 months, body weight did not change detectably in any of the treatment groups; however, body adiposity was reduced strikingly more by low-dose flutamide-metformin than by OC in monotherapy (Fig. 1, upper panels). In comparison to the girls on OC, those on flutamide-metformin lost a mean of approximately 4 kg of fat, and gained approximately 4 kg of lean mass within 9 months.

OC vs. OC plus flutamide-metformin in young PCOS women (Table 2)

In young women, the initiation of OC in monotherapy was followed by changes similar to those observed in teenagers on OC (hirsutism score, SHBG, testosterone, triglycerides, HDL cholesterol), including a lack of improvement in abnormal adipocytokine levels and a further increment of body adiposity.

In women receiving OC plus flutamide-metformin, the

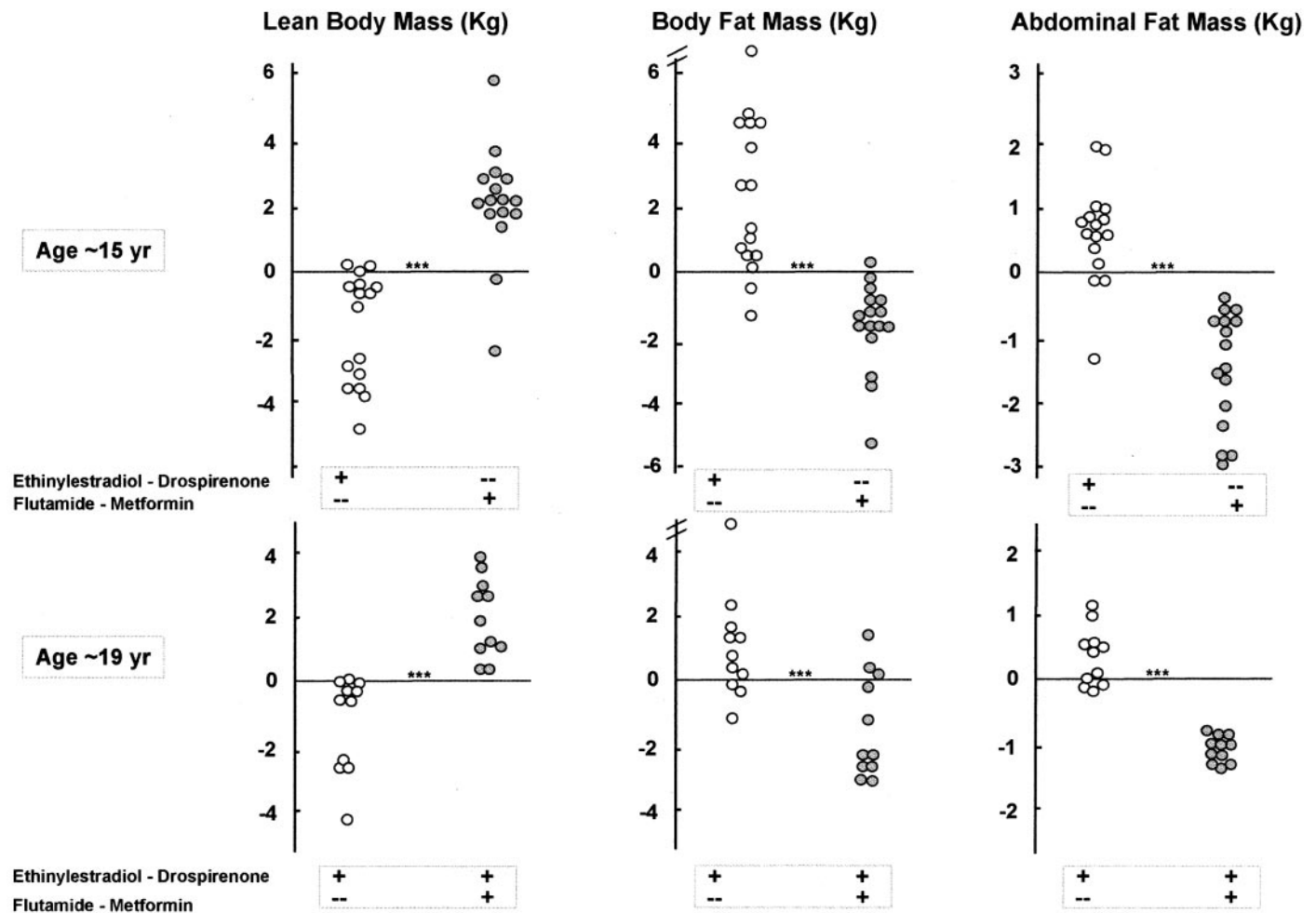


FIG. 1. Changes (0–9 months) in lean body mass, body fat mass, and abdominal fat mass in two PCOS populations. *Upper panels:* Teenage girls (age, ~15 yr; n = 32), randomized to receive either ethinylestradiol-drospirenone or flutamide-metformin. *Lower panels:* Young women (age, ~18 yr; n = 22), starting all on ethinylestradiol-drospirenone at time zero, and randomized to receive this either in monotherapy or together with flutamide-metformin. Subgroups receiving flutamide-metformin present more gain in lean body mass and more reduction in body fat mass, including in abdominal fat mass. ***, $P < 0.0001$.

changes in hirsutism score and in most endocrine-metabolic variables were similar to those in women on OC alone; however, the increment in SHBG and the drop in LDL cholesterol were more pronounced. In addition, both the adipocytokine pattern and the body composition changed favorably in the copresence of flutamide-metformin (Fig. 1, *lower panels*). Again, body weight remained virtually unchanged in each subgroup. However, when compared with young women on OC alone, the women receiving OC plus flutamide-metformin lost a mean of approximately 3 kg of fat and gained approximately 3 kg of lean mass in 9 months.

Discussion

Two major directions are emerging in the treatment of nonobese PCOS: one is an ovary-silencing strategy with estrogen-progestagen OCs, which also induce a rise of SHBG; the other uses insulin sensitization and/or androgen-receptor blockade (14–17, 33–36). Recently, each of these strategies has reached a novel milestone: on the OC side, ethinylestradiol-drospirenone is a fourth-generation monophasic OC that has been swiftly introduced into clinical practice; on the

other side, a low-dose duo of generics, flutamide and metformin, has been developed. These new treatments have now been compared with each other and with their own combination; the respective efficacies were mainly judged by impact on adipocytokemia and on body adiposity. Although central fat excess must long have been a concern for women with PCOS, it is only recently that their dramatic adiposity has been disclosed by DXA (4). In girls bound to develop nonobese PCOS, central fat already starts to accumulate in childhood, and this exaggeration of regional adipogenesis is known to be related to their hyperinsulinemic hyperandrogenism (5, 6, 30, 37–39).

In nonobese adolescents and young women, PCOS was now found to be an inflammation state with high levels of proinflammatory IL-6 and low levels of antiinflammatory adiponectin. The earlier observations that serum concentrations of CRP and IL-6 are elevated and those of adiponectin are reduced in obese women with PCOS (22, 40–43) are herewith extended into nonobese PCOS populations and into the age range of early adolescence.

In young teenagers with PCOS who were not at risk of

pregnancy, combined therapy with a minidose of flutamide and metformin (6) proved superior to monotherapy with a fourth-generation OC: the generic duo normalized serum triglycerides, LDL cholesterol, IL-6, and adiponectin, and reduced body adiposity. So far, the mechanism underpinning the efficacy of flutamide-metformin in reducing adiposity remained enigmatic, because this combination diminishes the circulating availability of anabolic hormones, including androgens, insulin, GH, and IGF-I (5). In the adolescents and in the young women studied here, there was a striking parallelism between the courses of body composition and adipocytokines, rather than between body adiposity and testosterone, SHBG, or fasting glucose-insulin ratio. Such a close parallelism suggests that the characteristic adiposity of young PCOS patients is tightly linked to their adipocytokine-lipid balance. If confirmed, the present findings imply that variables such as IL-6, adiponectin, triglycerides, and LDL cholesterol may prove to be more sensitive indices to monitor efficacy of PCOS therapy than classic endocrine markers, such as free androgen or baseline hyperinsulinemia. Both IL-6 and adiponectin are thought to be implicated in the pathogenesis or amplification of insulin resistance states, but the precise interlinkages remain to be fully disclosed (7–10, 44–46). It is known, however, that IL-6 and adiponectin modulate the metabolism of regional adipose tissue and relate more closely to central fat excess than to body weight (9, 22, 46–48).

In young women with PCOS, flutamide-metformin is known to increase ovulation rate (5), and this epiphenomenon of its efficacy implies a pregnancy risk. The present study evidenced that baseline therapy with low-dose flutamide-metformin can be complemented by a fourth-generation OC, as a safety measure. So far, a drospirenone-containing OC is preferred because, in contrast to a third-generation OC (6), it does not seem to inhibit the loss of abdominal fat, possibly because drospirenone has an activity spectrum close to that of natural progesterone (12, 49).

In conclusion, young and nonobese PCOS patients were found to be in a low-grade, chronic inflammation state and to have a body adiposity that evolves according to the balance of circulating adipocytokines and lipids, rather than to androgen excess or fasting hyperinsulinemia. Monotherapy with ethinylestradiol-drospirenone may not be a prime choice for PCOS, given its inefficacy to attenuate abnormal adipocytokine levels and body adiposity; however, ethinylestradiol-drospirenone plus flutamide-metformin is a first OC combination that was found capable of reverting both the adipocytokine balance and the body composition toward normal, and that may therefore improve the long-term cardiovascular perspectives of women with PCOS (50).

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