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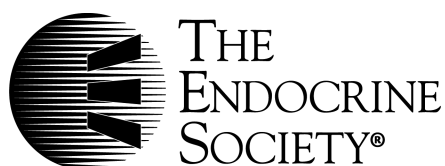
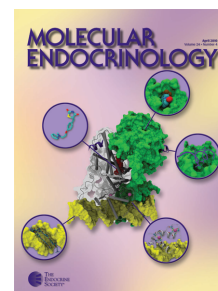
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Flutamide-Metformin plus Ethinylestradiol-Drospirenone for Lipolysis and Antiatherogenesis in Young Women with Ovarian Hyperandrogenism: The Key Role of Metformin at the Start and after More than One Year of Therapy

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Flutamide (Flu)-metformin (Met) with ethinylestradiol-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 ethinylestradiol-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. Fasting blood glucose, serum insulin, testosterone, lipid profile, adiponectin, and IL-6 were determined at the start and after 3 months, together with body composition, by dual energy x-ray absorptiometry.

The results of studies A and B complemented each other; the addition of Met was found to have consistently (more) normalizing effects on IL-6 and adiponectin, on lean mass (mean Met benefit of +1.2 kg in study A and +0.6 kg in study B), and in particular on abdominal fat excess [Met benefit of -0.7 kg (A) and -0.3 kg (B)].

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 stigmata 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 estrogen-progestagen 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 ethinylestradiol-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). Although there is emerging consensus about the need for insulin sensitization at the start of PCOS treatment (12–16), the additive benefits of Met remain to be shown in the copresence of Flu and an OC, as well in the initiation phase as after prolonged intake of such combination therapy.

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 \pm 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 μ U/ml; and 2) ovarian hyperandrogenism as defined by hirsutism (Ferriman-

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Abbreviations: BMI, Body mass index; CV, coefficient of variation; DHEAS, dehydroepiandrosterone sulfate; Flu, flutamide; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Met, metformin; OC, oral contraceptive; PCOS, polycystic ovary syndrome.

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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

	OC and Flu (+) Met (-) ^a		OC and Flu (+) Met (+) ^a		Change over 3 months	
	0 month	3 months	0 month	3 months	Met (-)	Met (+)
BMI (kg/m ²)	21.9 ± 0.7	22.0 ± 0.7	22.4 ± 0.5	22.5 ± 0.5	0.0 ± 0.1	0.1 ± 0.1
Fasting glucose/insulin ratio ^b	6.8 ± 0.7	7.3 ± 0.7	7.6 ± 0.7	7.2 ± 0.6	0.4 ± 0.7	-0.4 ± 0.7
SHBG (μg/dl)	0.9 ± 0.1	3.8 ± 0.3 ^d	0.7 ± 0.1	3.7 ± 0.3 ^d	2.9 ± 0.3	3.0 ± 0.3
Testosterone (ng/dl)	105 ± 11	52 ± 7 ^d	101 ± 15	47 ± 6 ^c	-51 ± 12	-53 ± 14
Androstenedione (ng/dl)	285 ± 24	224 ± 25 ^d	264 ± 22	199 ± 17 ^d	-61 ± 14	-64 ± 13
DHEAS (μg/dl)	233 ± 18	183 ± 13 ^d	278 ± 20	237 ± 17 ^c	-56 ± 13	-41 ± 15
LDL cholesterol (mg/dl)	98 ± 4	81 ± 4 ^c	97 ± 3	88 ± 5 ^d	-17 ± 5	-9 ± 6
HDL cholesterol (mg/dl)	54 ± 2	71 ± 3 ^d	48 ± 2	68 ± 5 ^d	17 ± 4	20 ± 4
Triglycerides (mg/dl)	81 ± 5	90 ± 8	82 ± 5	82 ± 10	9 ± 8	-0.4 ± 9
IL-6 (fg/ml)	884 ± 105	1043 ± 149	994 ± 93	664 ± 57 ^c	159 ± 120	-329 ± 98 ^e
Adiponectin (μg/ml)	9.2 ± 1.0	10.3 ± 1.1	10.4 ± 0.7	12.6 ± 0.8 ^c	1.1 ± 0.5	2.2 ± 0.6
Fat mass (kg)	19.4 ± 2.2	19.8 ± 2.3	21.7 ± 1.8	20.7 ± 1.7 ^d	0.4 ± 0.3	-1.0 ± 0.2 ^f
Abdominal fat mass (kg)	6.9 ± 0.8	6.9 ± 0.7	7.0 ± 0.5	6.2 ± 0.4 ^d	-0.1 ± 0.1	-0.8 ± 0.2 ^f
Lean mass (kg)	35.3 ± 0.9	35.2 ± 0.8	34.4 ± 1.0	35.5 ± 0.8 ^c	-0.1 ± 0.3	1.1 ± 0.4 ^e

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.

^a No significant differences between randomized subgroups at 0 month.

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

^c $P \leq 0.01$ and ^d $P \leq 0.001$ vs. 0 month.

^e $P \leq 0.01$ and ^f $P \leq 0.001$ for 0- to 3-month change vs. the Met (-) subgroup.

Gallwey score above 8); and high serum androstenedione, total testosterone, or free androgen index (testosterone × 100/SHBG); and a 17-hydroxyprogesterone hyperresponse (>160 ng/dl) to GnRH agonist (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, 15.4–25.7 kg/m²; 5–13 yr post menarche).

All patients had been diagnosed with hyperinsulinemic ovarian hyperandrogenism according to the criteria of Study A, and they had been treated with a combination of Met (850 mg/d) and Flu (62.5 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; informed 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).

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).

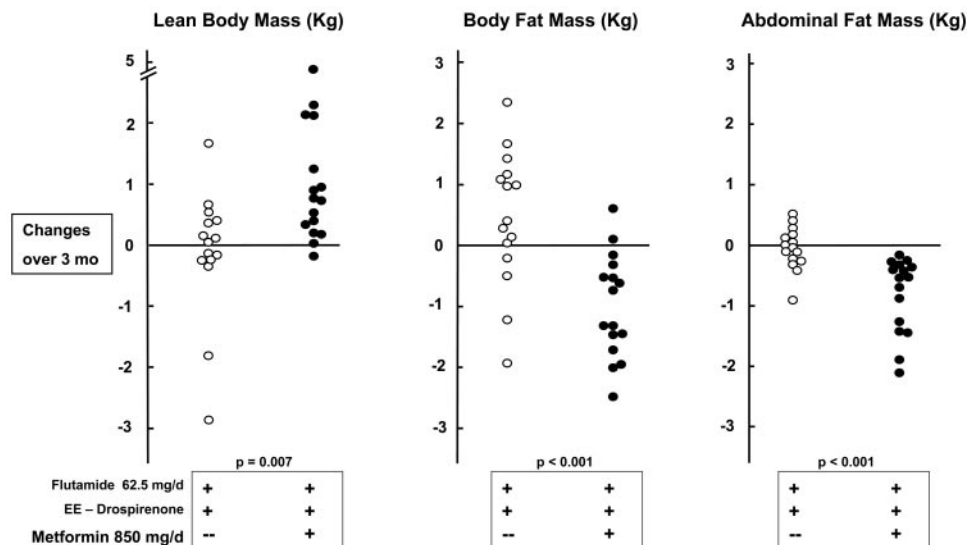


TABLE 2. Clinical, hormonal, cytokine, and dual-energy x-ray absorptiometry variables in young women (n = 42; age ~19 yr; height 159 cm; 5–13 yr post menarche) with hyperinsulinemic hyperandrogenism, who had been treated with Flu (62.5 mg/d) and Met (850 mg/d) together with an OC for an average of 17 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

	OC and Flu (+) Met (-) ^a		OC and Flu (+) Met (+) ^a		Change over 3 months	
	0 month	3 months	0 month	3 months	Met (-)	Met (+)
BMI (kg/m ²)	22.0 ± 0.6	22.1 ± 0.6	21.4 ± 0.5	21.4 ± 0.4	0.0 ± 0.1	0.0 ± 0.3
Fasting glucose/insulin ratio ^b	8.3 ± 0.8	8.7 ± 0.9	10.1 ± 0.8	9.2 ± 0.7	0.4 ± 0.9	-0.9 ± 0.6
SHBG (μg/dl)	3.7 ± 0.3	4.5 ± 0.3	4.1 ± 0.3	4.7 ± 0.2 ^d	0.8 ± 0.4	0.7 ± 0.2
Testosterone (ng/dl)	59 ± 6	57 ± 6	67 ± 8	48 ± 4 ^d	-2 ± 7	-19 ± 6
Androstenedione (ng/dl)	217 ± 18	215 ± 17	189 ± 13	194 ± 14	-2 ± 8	5 ± 7
DHEAS (μg/dl)	188 ± 17	182 ± 16	178 ± 16	159 ± 14 ^c	-7 ± 11	-19 ± 8
LDL cholesterol (mg/dl)	95 ± 6	97 ± 5	91 ± 6	86 ± 5	2 ± 4	-5 ± 5
HDL cholesterol (mg/dl)	73 ± 4	78 ± 4 ^c	74 ± 2	78 ± 4	5 ± 2	4 ± 4
Triglycerides (mg/dl)	86 ± 8	84 ± 7	89 ± 9	88 ± 7	-2 ± 9	-1 ± 7
IL-6 (fg/ml)	757 ± 65	834 ± 61	880 ± 117	735 ± 67	77 ± 47	-145 ± 104 ^h
Adiponectin (μg/ml)	10.7 ± 0.7	10.0 ± 0.6 ^e	9.5 ± 0.5	10.5 ± 3.4 ^c	-0.7 ± 0.3	1.0 ± 0.4 ^g
Fat mass (kg)	20.7 ± 1.3	20.9 ± 1.4	17.5 ± 1.2	17.2 ± 1.1	0.2 ± 0.3	-0.3 ± 0.2
Abdominal fat mass (kg)	4.9 ± 0.4	5.1 ± 0.4 ^c	4.4 ± 0.4	4.4 ± 0.3	0.2 ± 0.1	-0.1 ± 0.1 ^f
Lean mass (kg)	33.6 ± 1.0	33.5 ± 1.0	34.6 ± 1.1	35.1 ± 1.1 ^c	-0.1 ± 0.2	0.5 ± 0.1 ^g

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.

^a No significant differences between randomized subgroups at 0 month.

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

^c $P < 0.05$; ^d $P \leq 0.01$; and ^e $P \leq 0.001$ vs. 0 month.

^f $P < 0.05$; ^g $P \leq 0.01$; and (after log-transformation) ^h $P \leq 0.001$ for 0- to 3-month change vs. the Met (-) subgroup.

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 in addition [850 mg, once daily at dinner time, for 3 months; OC and Flu (+) Met (+); n = 16] or not [OC and Flu (+) Met (-); n = 15].

Study B

Patients receiving full combination therapy [OC and Flu (+) Met (+)] (8, 9) were randomized for maintenance of the combination (n = 22) or for discontinuation of Met [OC and Flu (+) Met (-); n = 20] during the subsequent 3 months.

Endocrine-metabolic assessment

Fasting blood glucose, serum insulin, lipid profile, SHBG, testosterone, androstenedione, dehydroepiandrosterone sulfate (DHEAS), adiponectin, and IL-6 were determined at baseline and after 3 months, together with indices of hepatic and renal function, as additional safety variables.

Body composition, assays, and statistics

Body composition was assessed by dual-energy x-ray absorptiometry at study start and after 3 months, with a Lunar Prodigy coupled to Lunar software (version 3.4/3.5, Lunar Corp., Madison, WI) (20). Absolute (kilograms) whole-body fat and lean 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) (21). Total irradiation dose per assessment was 0.1 mSv. Coefficients of variation (CVs) for scanning precision were 2.0% and 2.6% for fat and lean body mass (22); intraindividual CV for abdominal fat mass was 0.7%.

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%. Serum testosterone, androstenedione, DHEAS, 17-hydroxyprogesterone, and SHBG were assayed as described (5, 8). IL-6 was measured by immunochemiluminescence (Immulin 2000, Diagnostic Products, Los Angeles, CA), with a detection limit of 100 fg/ml; intra- and interassay CVs were 3.5% and 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, dysadipocytokemia, 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.

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 adjuvans 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 (31–35). 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 dysadipocytokemia, the lean mass deficit, and the central adiposity of young patients with PCOS.

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References

- Dunaif A, Thomas A 2000 Current concepts in the polycystic ovary syndrome. *Annu Rev Med* 52:401–419
- Baumann EE, Rosenfield RL 2002 Polycystic ovary syndrome in adolescence. *The Endocrinologist* 12:333–348
- Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale H 2000 A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *J Clin Endocrinol Metab* 85:2434–2438
- Kirchengast S, Huber J 2001 Body composition characteristics and body fat distribution in lean women with polycystic ovary syndrome. *Hum Reprod* 16:1255–1260
- Ibáñez L, Ong K, Ferrer A, Amin R, Dunger D, de Zegher F 2003 Low-dose flutamide-metformin therapy reverses insulin resistance and reduces fat mass in non-obese adolescents and young women with ovarian hyperandrogenism. *J Clin Endocrinol Metab* 88:2600–2606
- Ibáñez L, de Zegher F 2003 Flutamide-metformin to reduce fat mass in hyperinsulinemic ovarian hyperandrogenism: effects in adolescents and in women on third-generation oral contraception. *J Clin Endocrinol Metab* 88:4720–4724
- Morin-Papunen L, Rautio K, Ruokonen A, Hedberg P, Puukka M, Tapanaainen JS 2003 Metformin reduces serum C-reactive protein levels in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 88:4649–4654
- Ibáñez L, de Zegher F 2004 Ethinylestradiol-drospirenone, flutamide-metformin, or both for adolescents and young women with hyperinsulinemic hyperandrogenism: opposite effects on adipocytokines and body adiposity. *J Clin Endocrinol Metab* 89:1592–1597
- Ibáñez L, Valls C, Cabré S, de Zegher F 2004 Flutamide-metformin plus ethinylestradiol-drospirenone for lipolysis and anti-atherogenesis in young women with ovarian hyperandrogenism: the key role of early, low-dose flutamide. *J Clin Endocrinol Metab* 89:4716–4720
- Ibáñez L, de Zegher F 2004 Flutamide-metformin plus an oral contraceptive (OC) for young women with polycystic ovary syndrome: switch from third- to fourth-generation OC reduces body adiposity. *Hum Reprod* 19:1725–1727
- Ibáñez L, Valls C, Ferrer A, Ong K, Dunger D, de Zegher F 2002 Additive effects of insulin-sensitizing and antiandrogen treatment in young, nonobese women with hyperinsulinism, hyperandrogenism, dyslipidemia and anovulation. *J Clin Endocrinol Metab* 87:2870–2874
- Nestler JE 2002 Should patients with polycystic ovary syndrome be treated with metformin? An enthusiastic endorsement. *Hum Reprod* 17:1950–1953
- de Leo V, La Marca A, Petraglia F 2003 Insulin-lowering agents in the management of polycystic ovary syndrome. *Endocr Rev* 24:633–667
- Costello MF, Eden JA 2003 A systematic review of the reproductive system effects of metformin in patients with polycystic ovary syndrome. *Fertil Steril* 79:1–13
- Diamanti-Kandarakis E, Baillargeon JP, Iuorno MJ, Jakubowicz DJ, Nestler JE 2003 Controversies in endocrinology. A modern medical quandary: polycystic ovary syndrome, insulin resistance, and oral contraceptive pills. *J Clin Endocrinol Metab* 88:1927–1932
- Homburg R, Lambalk CB 2004 Debate: polycystic ovary syndrome in adolescence—a therapeutic conundrum. *Hum Reprod* 19:1–4
- The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997 Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197
- New MI, Lorenzen F, Lerner AJ, Kohn B, Oberfield SE, Pollack MS, Dupont B, Stoner E, Levy DJ, Pang S, Levine LS 1983 Genotyping steroid 21-hydroxylase deficiency: hormonal reference data. *J Clin Endocrinol Metab* 56:320–325
- Sakkal-Alkaddour H, Zhang L, Yang X, Chang YT, Kappy M, Slover RS 1996 Studies of β -hydroxysteroid dehydrogenase genes in infants and children manifesting premature pubarche and increased adrenocorticotropic-stimulated Δ 5-steroid levels. *J Clin Endocrinol Metab* 81:3961–3965
- Ibáñez L, Ong K, de Zegher F, Marcos MV, del Rio L, Dunger D 2003 Fat distribution in non-obese girls with and without precocious pubarche: central adiposity related to insulinemia and androgenemia from pre-puberty to post-menarche. *Clin Endocrinol (Oxf)* 58:372–379
- Taylor RW, Keil D, Gold EJ, Williams SM, Goulding A 1998 Body mass index, waist girth, and waist-to-hip ratio as indexes of total and regional adiposity in women: evaluation using receiver operating characteristic curves. *Am J Clin Nutr* 67:44–49
- Kiebzak GM, Leamy LJ, Pierson LM, Nord RH, Zhang ZY 2000 Measurement precision of body composition variables using the Lunar DPX-L densitometer. *J Clin Densitom* 3:35–41
- Rexrode KM, Pradhan A, Manson JE, Buring JE, Ridker PM 2003 Relationship of total and abdominal adiposity with CRP and IL-6 in women. *Ann Epidemiol* 13:674–682
- Ferreira I, Twisk JW, van Mechelen W, Kemper HC, Seidell JC, Stehouwer CD 2004 Current and adolescent body fatness and fat distribution: relationships with carotid intima-media thickness and large artery stiffness at the age of 36 years. *J Hypertens* 22:145–155
- Ferreira I, Snijder MB, Twisk JWR, van Mechelen W, Kemper HCG, Seidell JC, Stehouwer CDA 2004 Central fat mass versus peripheral fat and lean mass: opposite (adverse versus favorable) associations with arterial stiffness? The Amsterdam Growth and Health Longitudinal Study. *J Clin Endocrinol Metab* 89:2632–2639
- Goldstein BJ, Scalia R 2004 Adiponectin: a novel adipokine linking adipocytes and vascular function. *J Clin Endocrinol Metab* 89:2563–2568
- Pittas AG, Joseph NA, Greenberg AS 2004 Hot topic: adipocytokines and insulin resistance. *J Clin Endocrinol Metab* 89:447–452
- Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sheedy II PF, Fitz-

- patrick LA 2003 Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 88:2562–2568
29. Elting MW, Korsen TJM, Bezemer PD, Schoemaker J 2001 Prevalence of diabetes mellitus, hypertension and cardiac complaints in a follow-up study of a Dutch PCOS population. *Hum Reprod* 16:556–560
30. Lakhani K, Seifalian AM, Hardiman P 2002 Impaired carotid viscoelastic properties in women with polycystic ovaries. *Circulation* 106:81–85
31. Ibáñez L, Valls C, Potau N, Marcos MV, de Zegher F 2000 Sensitization to insulin in adolescent girls to normalize hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism after precocious pubarche. *J Clin Endocrinol Metab* 85:3526–3530
32. Nestler JE, Jakubowicz DJ 1997 Lean women with polycystic ovary syndrome respond to insulin reduction with decreases in ovarian P450c17 α activity and serum androgens. *J Clin Endocrinol Metab* 82:4075–4079
33. Morin-Papunen L, Vauhkonen I, Koivunen R, Ruokonen A, Martikainen H, Tapanainen JS 2003 Metformin versus ethinyl estradiol-cyproterone acetate in the treatment of nonobese women with polycystic ovary syndrome: a randomized study. *J Clin Endocrinol Metab* 88:148–156
34. Ibáñez L, Ferrer A, Ong K, Amin R, Dunger D, de Zegher F 2004 Insulin sensitization early post-menarche prevents progression from precocious pubarche to polycystic ovary syndrome. *J Pediatr* 144:23–29
35. Ibáñez L, Valls C, Marcos MV, Ong K, Dunger D, de Zegher F 2004 Insulin sensitization for girls with precocious pubarche and with risk for polycystic ovary syndrome: effects of prepubertal initiation and postpubertal discontinuation of metformin. *J Clin Endocrinol Metab* 89:4331–4337

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