0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(7):2453–2461

doi: 10.1210/jc.2007-0282

Comparison of Ethinyl-Estradiol Plus Cyproterone Acetate *Versus* Metformin Effects on Classic Metabolic Cardiovascular Risk Factors in Women with the Polycystic Ovary Syndrome

Manuel Luque-Ramírez, Francisco Álvarez-Blasco, José I. Botella-Carretero, Elena Martínez-Bermejo, Miguel A. Lasunción, and Héctor F. Escobar-Morreale

Departments of Endocrinology (M.L.-R., F.A.-B., J.I.B.-C., E.M.-B., H.F.E.-M.) and Biochemistry-Research (M.A.L.), Hospital Universitario Ramón y Cajal and Universidad de Alcalá, E-28034 Madrid, Spain; and Centro de Investigación Biomédica en Red (CIBER) Fisiopatologia Obesidad y Nutrición (CB06/03) (M.A.L.), Instituto de Salud Carlos III, E-28029 Madrid, Spain

Context: Oral contraceptives may worsen the metabolic profile of patients with polycystic ovary syndrome (PCOS), favoring the use of insulin sensitizers in these patients.

Objective: The aim of the study was to compare the effects of a contraceptive pill on metabolic classic cardiovascular risk factors with those of the insulin sensitizer metformin.

Design: We conducted a randomized, parallel, open-label clinical trial.

Setting: The study was conducted at an academic hospital.

Patients: Thirty-four consecutive PCOS patients were studied.

Interventions: Patients were randomized to oral treatment with metformin (850 mg twice daily) or with the Diane^{35} Diario pill (35 μg of ethinyl-estradiol plus 2 mg of cyproterone acetate) for 24 wk.

Main Outcome Measures: Hyperandrogenism, lipid profiles, and indexes of glucose tolerance and insulin sensitivity were measured at baseline and after 12 and 24 wk of treatment.

Results: Diane^{35} Diario resulted in higher reductions in hirsutism score and serum androgen levels compared with metformin. Menstrual regularity was restored in all the patients treated with Diane^{35} Diario compared with only 50% of those receiving metformin. Plasma apolipoprotein A-I and HDL-phospholipid levels increased with Diane^{35} Diario, whereas metformin did not induce any change in the lipid profile. On the contrary, the insulin sensitivity index increased with metformin but did not change with Diane^{35} Diario. No differences in the frequencies of abnormalities of glucose tolerance and dyslipidemia were found between both treatments.

Conclusions: Diane^{35} Diario appears to be superior to metformin for the control of hyperandrogenism and for the restoration of menstrual regularity in PCOS patients, and it is not associated with any clinically relevant worsening in the classic metabolic cardiovascular risk profile of these women. **(*J Clin Endocrinol Metab* 92: 2453–2461, 2007)**

THE POLYCYSTIC OVARY syndrome (PCOS) is a common endocrine disorder of premenopausal women (1, 2), characterized by the presence of hyperandrogenism together with ovulatory dysfunction and/or polycystic ovarian morphology (3).

Although the primary defect in PCOS appears to be an exaggerated androgen synthesis and secretion (4), particularly by ovarian theca cells (5), insulin resistance and obesity may act as triggers of this primary defect (6), explaining the frequent association of PCOS with obesity (6, 7) and with insulin resistance (8).

Cardiovascular risk factors cluster in patients with PCOS and their families, although the demonstration of an increase in cardiovascular morbidity or mortality in these patients is still lacking (9). PCOS patients present increased frequencies of glucose intolerance (up to 30–35%) and type 2 diabetes (7 to 10%) (10, 11), gestational diabetes (12, 13), an unfavorable lipid profile characterized by decreased high-density lipoprotein (HDL)-cholesterol and increased triglycerides levels (14, 15), and even increased low-density lipoprotein (LDL)-cholesterol (16, 17) and an increased risk for hypertension (18). In conceptual agreement, the prevalence of the metabolic syndrome is increased in PCOS patients (19, 20), although this finding may result from the frequent association with obesity (7).

In recent years, the clustering of cardiovascular risk factors in PCOS patients raised concern about the optimal drug therapy for this disorder. Aside from essential lifestyle recommendations and diet in women with weight excess (21) and from therapeutic strategies directed toward restoration of fertility, the chronic pharmacological treatment of PCOS is based on the use of two families of drugs, namely oral contraceptives containing a progestin of low androgenicity or even antiandrogenic properties, or insulin sensitizers.

Oral contraceptives have been the mainstay of PCOS pharmacological therapy for decades (22). However, in nonhy-

First Published Online April 10, 2007

Abbreviations: Apo, Apolipoprotein; AUC, area(s) under the curve; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; oGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

perandrogenic women oral contraceptives might adversely influence insulin resistance and glucose tolerance, raising concern about a possible worsening of the unfavorable metabolic cardiovascular risk profile of PCOS patients and favoring the use of the metabolically safer insulin-sensitizer drugs (23).

Yet at present there is not enough scientifically sound evidence supporting this recommendation (24). The present study summarizes the results of a randomized clinical trial comparing the effects of an antiandrogenic low-dose oral contraceptive pill with those of the insulin sensitizer metformin on the classic metabolic cardiovascular risk factors of PCOS patients.

Patients and Methods

Patients

The present study is the first report of a broader project aiming to compare systematically the effects of an oral contraceptive and metformin on classic and nonclassic cardiovascular risk factors and on several indexes of cardiovascular function and performance, by using a randomized, open-label, parallel clinical trial comparing both treatments (www.clinicaltrials.gov; NLM Identifier NCT00428311).

Thirty-four consecutive PCOS patients were recruited. The diagnosis of PCOS was based on the presence of clinical and/or biochemical hyperandrogenism, oligoovulation, and exclusion of secondary etiologies (3, 25). Hirsutism was defined by a modified Ferriman-Gallwey score above 7 (26) and oligomenorrhea (more than six cycles longer than 36 d in the previous year) or amenorrhea (absence of menstruation for 3 consecutive months) (27), or luteal phase progesterone measurements less than 4 ng/ml (12.72 nmol/liter) in women with regular menstrual cycles were considered indicative of oligoovulation. Secondary etiologies, including hyperprolactinemia, thyroid dysfunction, Cushing's syndrome, congenital adrenal hyperplasia, and virilizing tumors, were actively ruled out in all the patients.

None of the patients had a personal history of hypertension, diabetes mellitus, or cardiovascular events, or received treatment with oral contraceptives, antiandrogens, insulin sensitizers, or drugs that might interfere with blood pressure regulation, lipid profile, or carbohydrate metabolism for the previous 6 months. Written informed consent was obtained from all the participants or their legal representatives, and the study was approved by the local ethics committee and by the Spanish Agency of Medicines.

Interventions

After providing informed consent, patients were randomized to receive an antiandrogenic low-dose oral contraceptive pill in cycles of 28 d (21 pills containing 35 μg of ethinyl-estradiol plus 2 mg of cyproterone acetate followed by 7 placebo pills, Diane^{35} Diario; Schering España S.A., Madrid, Spain), or 850 mg of metformin (Dianben; Merck Farma y Química S.A., Mollet del Vallés, Barcelona, Spain) twice daily for 24 wk. Simple randomization was conducted using blocks of 10 sealed opaque envelopes assigning five patients to receive Diane^{35} Diario and five patients to receive metformin. One investigator generated the randomization envelopes, whereas another enrolled and assigned the participants to their arm of treatment. No masking method was used after randomization.

Treatment was started the first day of a spontaneous menstrual cycle or, in women with amenorrhea, after excluding pregnancy by proper testing. Metformin was started at a 425-mg dose twice daily during the first week of treatment with the aim of minimizing gastrointestinal side effects. Women randomized to metformin were advised to use barrier contraception throughout the study. All the patients were instructed to maintain a diet containing 25–30 kcal per kg of body weight per day and moderate physical activity throughout the trial, although these measures were not stressed thereafter.

Main outcome measurements

A single investigator (M.L.-R.) was responsible for clinical, anthropometric, and physical evaluations at baseline and after 12 and 24 wk of treatment. Clinical and anthropometrical variables included the above-mentioned hirsutism score, body mass index (BMI), waist circumference, and waist to-hip ratio. The latter was calculated by dividing the minimal waist circumference by the hip circumference at the level of greater trochanters, using a nonstretchable measuring tape. The percentage of body fat with respect to total body weight was estimated using a body fat monitor (Omron BF 300; Omron Corp., Kyoto, Japan).

Serum and plasma samples were obtained between d 5 and 10 of a spontaneous menstrual bleeding or after excluding pregnancy in amenorrheic patients. After a 3-d 300-g carbohydrate diet and 12-h overnight fasting, basal samples were obtained for measurement of an androgenic profile consisting in serum free testosterone, androstenedione, and dehydroepiandrosterone sulfate concentrations (3). Then, a 75-g oral glucose tolerance test (oGTT) was performed, and samples were obtained for measurement of serum insulin and plasma glucose at 0, 30, 60, 90, and 120 min. Samples were immediately centrifuged, and serum was separated and frozen at − 30 C until assayed.

The technical characteristics of the assays employed for plasma glucose and serum hormone measurements have been described elsewhere (28, 29). Free testosterone levels were calculated from total testosterone and SHBG concentrations (30). The composite insulin sensitivity index was calculated from the circulating glucose and insulin concentrations during the oGTT (31). The areas under the curve (AUC) for glucose and insulin during the oGTT were determined according to the mathematical method described by Tai (32).

Disorders of glucose tolerance were defined from the circulating glucose concentrations at 0 and 120 min during oGTT according to the criteria of the American Diabetes Association (33). Circulating HDL-cholesterol and phospholipid levels were measured by enzymatic methods after precipitation of plasma with phosphotungstic acid and Mg^{2+} (Roche Molecular Biochemicals GmbH, Mannheim, Germany). Total cholesterol and triglyceride levels were determined by enzymatic methods (Menarini Diagnostica, Florence, Italy). LDL-cholesterol concentrations were estimated by Friedewald's equation (34). Circulating apolipoprotein (Apo) AI, Apo B100, and lipoprotein (a) levels were determined by kinetic immunonephelometry (Dade Behring, Deerfield, IL). The diagnosis of dyslipidemia was established according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III guidelines (35).

Statistical analysis

Data are shown as means ± SD and raw numbers (percentages) unless otherwise stated. The differences in frequencies among groups were analyzed by χ^2 or Fisher's exact tests as appropriate. The changes in the frequencies of metabolic disorders during the study were analyzed by McNemar's test, applying a Bonferroni correction to the level of significance to correct for multiple comparisons.

For continuous variables, normality was assessed by the Kolmogorov-Smirnov test, and logarithmic or square root transformations were applied as needed to ensure normality. The baseline characteristics of the patients randomized to receive Diane^{35} Diario or metformin were compared by unpaired *t* test. Data were submitted to a repeated-measures general lineal model including the arm of treatment as the between-subjects effect, and the visit (baseline, 12 and 24 wk) as the within-subjects effect. To evaluate the differences in the response to each treatment, the interaction between the between-subjects and within-subjects effect was calculated.

A priori sample size analysis was performed using the online calculator provided by the Massachusetts General Hospital Mallinckrodt General Clinical Research Center (http://hedwig.mgh.harvard.edu/sample_size/size.html). Because the possible advantages of metformin over Diane^{35} Diario rely on the presumed opposite effects of both drugs on insulin resistance, we used the difference in surrogate markers of insulin resistance as the primary outcome for sample size analysis. An experimental design including a total of 22 patients would have power above 0.80 to detect differences in fasting insulin levels between treatments such as those previously reported using a similar experimental design (36, 37).

Because seven patients discontinued metformin for different reasons (Fig. 1), results obtained when considering only the patients completing the three visits of the protocol were also confirmed by intention-to-treat analysis assuming, for patients who did not complete the study, that the dependent variables had not changed at the missing visits with respect to the values observed in the previous visit. $P < 0.05$ was considered statistically significant. Other than sample size calculations, analyses were performed using SPSS 10.0 for Macintosh (SPSS Inc., Chicago, IL).

Results

Recruitment and flow of the study

The study was conducted from April 2004 to December 2006. Thirty-four PCOS patients (age 24 ± 6 yr; BMI 30.0 ± 6.3 kg/m^2; nine had a BMI < 25 kg/m^2, 10 had a BMI 25–29.9 kg/m^2, and 15 had a BMI ≥ 30 kg/m^2) agreed to participate and, after giving written informed consent, were randomized to receive Diane^{35} Diario or metformin. The baseline characteristics of each group are summarized in Table 1, showing no differences among the patients randomized to each drug. All the patients treated with Diane^{35} Diario completed the study, whereas seven of the 19 patients assigned to metformin (37%) did not complete the study for the reasons detailed in Fig. 1. Of those, mild to moderate gastrointestinal side effects of metformin were responsible for the dropout in two women, whereas Diane^{35} Diario was well tolerated by all the women.

Effects of treatments on clinical characteristics and serum androgen profile

There were no differences with respect to baseline in BMI, waist circumference, waist to hip ratio, and fat mass expressed as percentage of body weight (Fig. 2). When considering PCOS patients as a whole, the hirsutism score and serum free testosterone and androstenedione levels decreased with treatment (Fig. 2), yet detailed analysis of the interaction between the within- and between-subjects effects of the general linear model revealed that these differences resulted mostly from the decrease observed in the patients treated with Diane^{35} Diario, which was much more marked than those observed with metformin (Fig. 2). Similarly, only treatment with Diane^{35} Diario induced a decrease in serum dehydroepiandrosterone sulfate levels (Fig. 2). Finally, at the end of the study, menstrual regularity was restored as expected in all the patients on Diane^{35} Diario but only in six patients (50%) on metformin.

Effects of treatments on the lipid profile

As occurred with clinical and biochemical hyperandrogenism, the changes observed in the lipid profile were mainly related to the effects of Diane^{35} Diario. In the women treated with this drug, plasma Apo A-I and HDL-phospholipid concentrations increased significantly, explaining the increase observed in these lipids, and in plasma HDL-cholesterol concentrations, in the whole group of patients when compared with baseline values (Fig. 3). On the contrary, no statistically significant changes were observed in plasma total and LDL-cholesterol, triglycerides, Apo B100, and lipoprotein (a) levels compared with baseline concentrations (Fig. 3).

Effects of treatments on indexes of glucose tolerance and insulin sensitivity

Indexes of insulin sensitivity improved in the whole series of PCOS patients, as the insulin sensitivity index increased, and fasting insulin and the insulin AUC during the oGTT decreased, compared with baseline (Fig. 4). Of these changes, only the increase in the insulin sensitivity index was specifically related to the metformin arm (Fig. 4), as suggested by a statistically significant interaction in the general linear model in the analysis of patients completing the study (although this particular interaction was not confirmed by the intention-to-treat analysis). On the contrary, fasting glucose

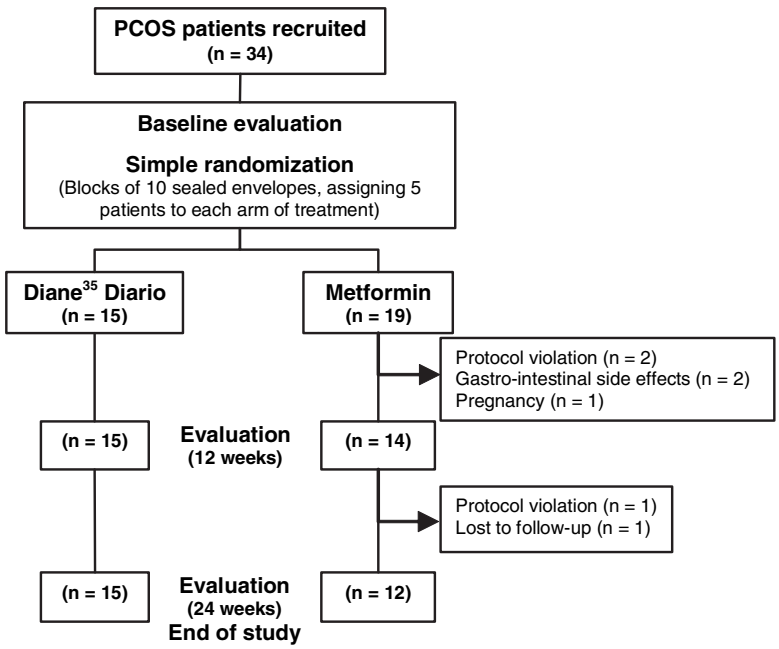

FIG. 1. Flow of the study.

TABLE 1. Baseline characteristics of the patients randomized to receive Diane^{35} Diario or metformin

	Diane^{35} Diario (n = 15)	Metformin (n = 19)	*P* value
Age (yr)	23.4 ± 5.6	25.1 ± 6.6	0.445
Smokers, n (%)	6 (40)	8 (42)	0.901
BMI (kg/m^2)	29.2 ± 5.7	30.5 ± 6.9	0.563
Waist circumference (cm)	83 ± 12	89 ± 18	0.306
Waist to hip ratio	0.79 ± 0.06	0.82 ± 0.11	0.292
Fat mass (% of body weight)	33 ± 6	34 ± 8	0.759
Hirsutism score	11 ± 5	10 ± 6	0.629
Free testosterone (ng/dl)	1.1 ± 0.4	1.3 ± 0.6	0.210
Androstenedione (ng/ml)	3.5 ± 0.8	3.9 ± 1.1	0.226
Dehydroepiandrosterone sulfate (ng/ml)	2,738 ± 1,022	2,250 ± 933	0.156
Total cholesterol (mg/dl)	154 ± 20	159 ± 28	0.529
HDL-cholesterol (mg/dl)	39 ± 11	41 ± 11	0.536
HDL-phospholipids (mg/dl)	100 ± 18	108 ± 17	0.244
LDL-cholesterol (mg/dl)	95 ± 19	101 ± 28	0.459
Triglycerides (mg/dl)	106 ± 96	89 ± 45	0.548
Apo A-I (mg/dl)	125 ± 18	129 ± 18	0.556
Apo B100 (mg/dl)	76 ± 22	83 ± 20	0.376
Lipoprotein (a) (mg/dl)	14 ± 23	29 ± 33	0.132
Fasting glucose (mg/dl)	93 ± 8	93 ± 8	0.993
Fasting insulin (μIU/ml)	14 ± 11	18 ± 16	0.429
AUC glucose (mg/dl·120 min)	15,143 ± 2,263	15,982 ± 4,080	0.529
AUC insulin (μIU/ml·120 min)	9,923 ± 5,793	10,158 ± 5,684	0.906
Insulin sensitivity index	4.4 ± 3.5	3.8 ± 2.4	0.564

Data are expressed as means ± SD, or raw numbers (percent). Data were submitted to unpaired *t* test or to χ^2 test, as appropriate. To convert to SI units, multiply free testosterone by 34.67 (result in pmol/liter), androstenedione by 3.49 (result in nmol/liter), dehydroepiandrosterone sulfate by 0.002714 (result in μmol/liter), cholesterol by 0.0259 (result in mmol/liter), triglycerides by 0.0113 (result in mmol/liter), glucose by 0.0555 (result in mmol/liter) and insulin by 6.945 (result in pmol/liter). AUC, Area under the curve during the oGTT.

and the glucose AUC during the oGTT showed no changes with respect to baseline values in the whole series of PCOS patients, although fasting glucose increased slightly in the patients treated with Diane^{35} Diario at the end of the study, compared with the evaluations performed at baseline and after 12 wk of treatment (Fig. 4).

Frequencies of disorders of glucose tolerance and dyslipidemia at baseline and throughout the study

There were no statistically significant differences in the frequencies of disorders of glucose tolerance and dyslipidemia between the arms of treatment, or at baseline and after 12 or 24 wk of treatment either when considering PCOS patients as a whole or when considering each arm of treatment separately (Table 2).

Of note, both the increase in patients with impaired fasting glucose and the decrease in the number of patients with low HDL-cholesterol levels after treatment with Diane^{35} Diario were far from reaching statistical significance. Also, it should be noted that in the two patients who developed impaired fasting glucose after treatment with Diane^{35} Diario, fasting glucose was minimally increased, *i.e.* to 100 mg/dl and 101 mg/dl (5.6 mmol/liter) respectively, and there was another patient who presented with impaired fasting glucose at baseline that returned to normal fasting glucose levels after treatment with the oral contraceptive. Similarly, the changes in glucose tolerance in the patients treated with metformin did not follow a discernible pattern despite the improvement in insulin resistance observed in these women as a group. Whereas normalization of glucose tolerance after 24 wk of treatment with metformin was observed in the patient with type 2 diabetes, in another patient with impaired glucose tolerance and in two of the women presenting with impaired fasting glucose, one patient presenting with normal glucose tolerance at baseline developed impaired fasting glucose and another woman developed impaired glucose tolerance after this treatment.

Discussion

Our present results confirm that both Diane^{35} Diario and metformin are safe and effective in the treatment of PCOS patients, both drugs showing overall beneficial effects on most of the clinical complaints characteristic of this common disorder. However, our data also suggest that Diane^{35} Diario is a more efficient way of treating hyperandrogenism and menstrual dysfunction, considering that the improvement in hirsutism, the amelioration of hyperandrogenemia, and the restoration of regular menstrual cycles occur earlier and more frequently with Diane^{35} Diario than with metformin.

On the other hand, although metformin clearly outperforms Diane^{35} Diario in improving insulin resistance, our present data indicate that Diane^{35} Diario is a safe drug when considering classic metabolic cardiovascular risk factors, and might even have favorable effects on the lipid profile of PCOS patients. To this regard, whereas the improvement in insulin resistance found with metformin was not related to any change in the lipid profile of PCOS patients, Diane^{35} Diario actually induced an increase in plasma Apo A-I and HDL-phospholipid levels, explaining the increase in plasma HDL-cholesterol concentrations observed in the whole group of PCOS patients. This finding is especially important considering that decreased HDL-cholesterol levels are among the commonest lipid abnormalities associated with

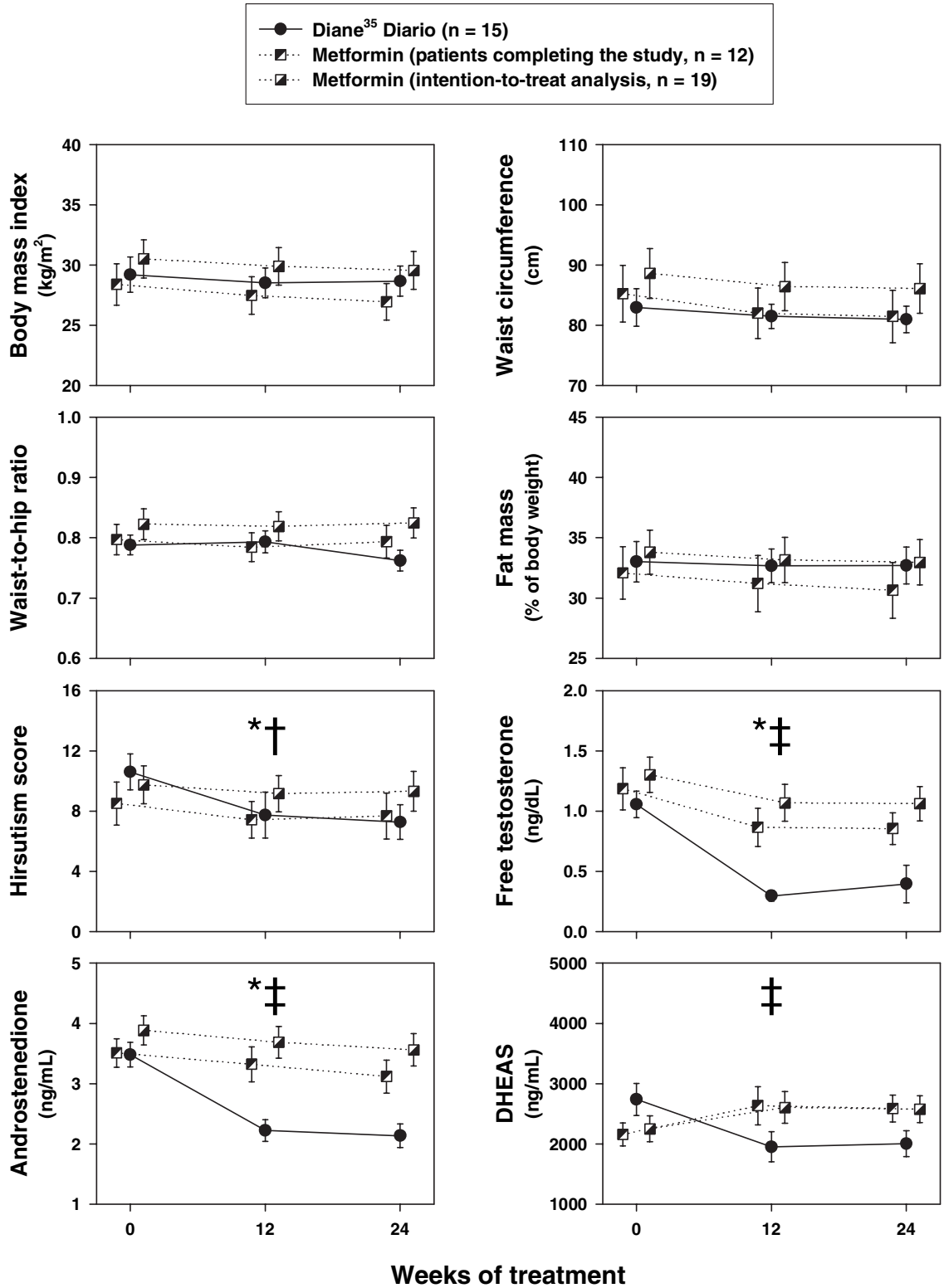

FIG. 2. Changes in clinical characteristics and serum androgen profiles of PCOS patients submitted to treatment with Diane^{35} Diario or metformin for 24 wk. Data are expressed as means ± SEM. Because of the large dropout rate in the metformin arm, the figures show the analysis of the patients completing the study (n = 12) and also an intention-to-treat analysis including all the patients treated with metformin (n = 19), yet assuming for patients who did not complete the study that the dependent variables did not change at the missing visits with respect to the values observed in the previous visit. DHEAS, Dehydroepiandrosterone-sulfate. *, $P < 0.05$ compared with baseline values in the whole group of patients, irrespective of the arm of treatment. †, $P < 0.05$ for the differences in the changes of each variable depending on the arm of treatment, only in the intention-to-treat analysis. ‡, $P < 0.05$ for the differences in the changes of each variable depending on the arm of treatment, both by analysis of patients who completed the study and by intention-to-treat analysis.

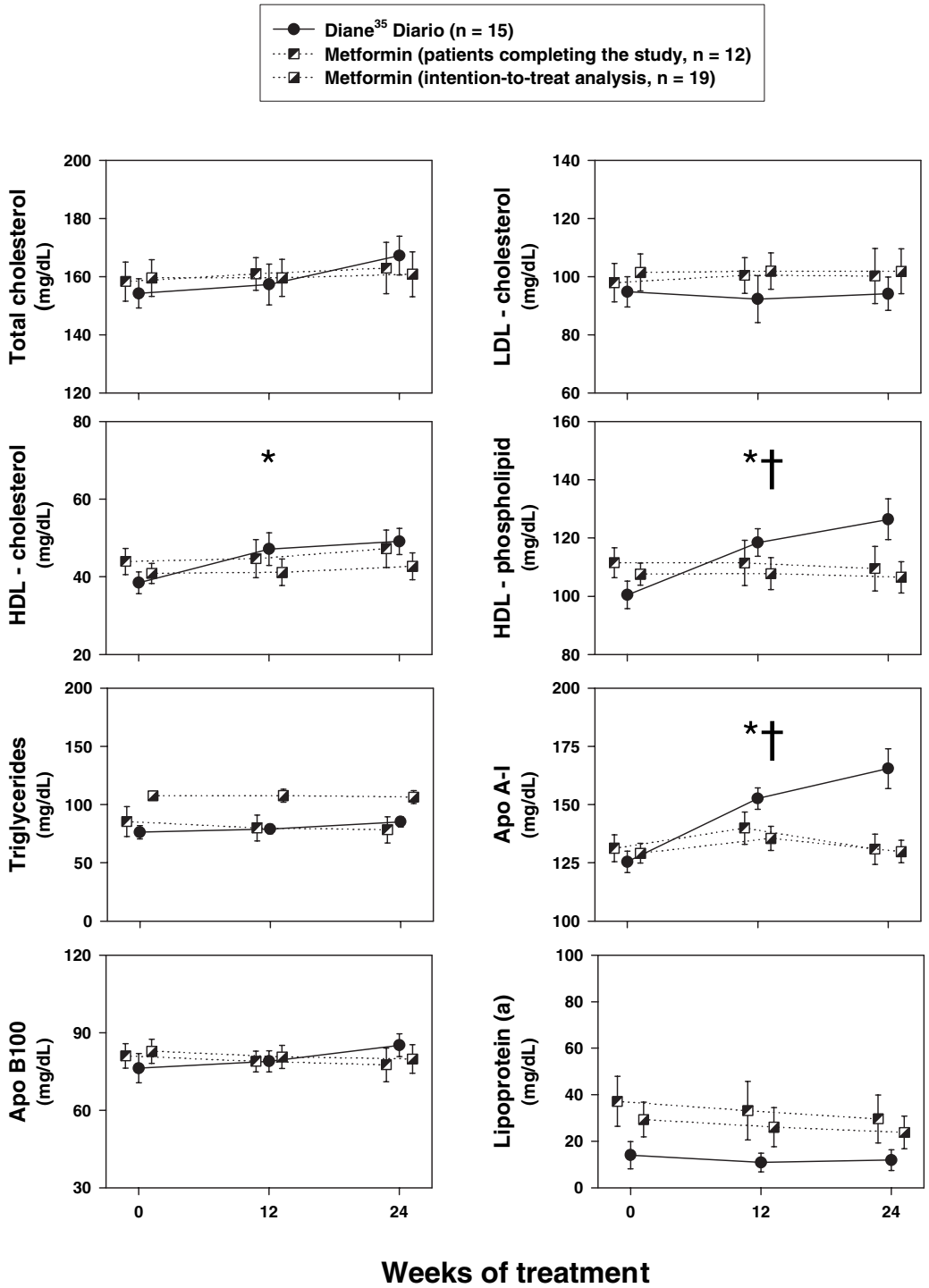

FIG. 3. Changes in the lipid profile of PCOS patients submitted to treatment with Diane[35] Diario or metformin for 24 wk. Data are expressed as means ± SEM. Because of the large dropout rate in the metformin arm, the figures show the analysis of the patients completing the study (n = 12) and also an intention-to-treat analysis including all the patients treated with metformin (n = 19), yet assuming for patients who did not complete the study that the dependent variables did not change at the missing visits with respect to the values observed in the previous visit. *, $P < 0.05$ compared with baseline values in the whole group of patients, irrespective of the arm of treatment. †, $P < 0.05$ for the differences in the changes of each variable depending on the arm of treatment, both by analysis of patients who completed the study and by intention-to-treat analysis.

PCOS (14, 15) and are a recognized cardiovascular risk factor (38). Furthermore, similar results have been reported earlier in the few studies actually comparing metformin with the particular oral contraceptive formulation used here (39, 40).

Considering our present finding with those reported by others, it appears that Diane[35] Diario has an effect on the regulation of HDL-cholesterol metabolism. This possibly involves the activity of plasma hepatic lipase activity, an en-

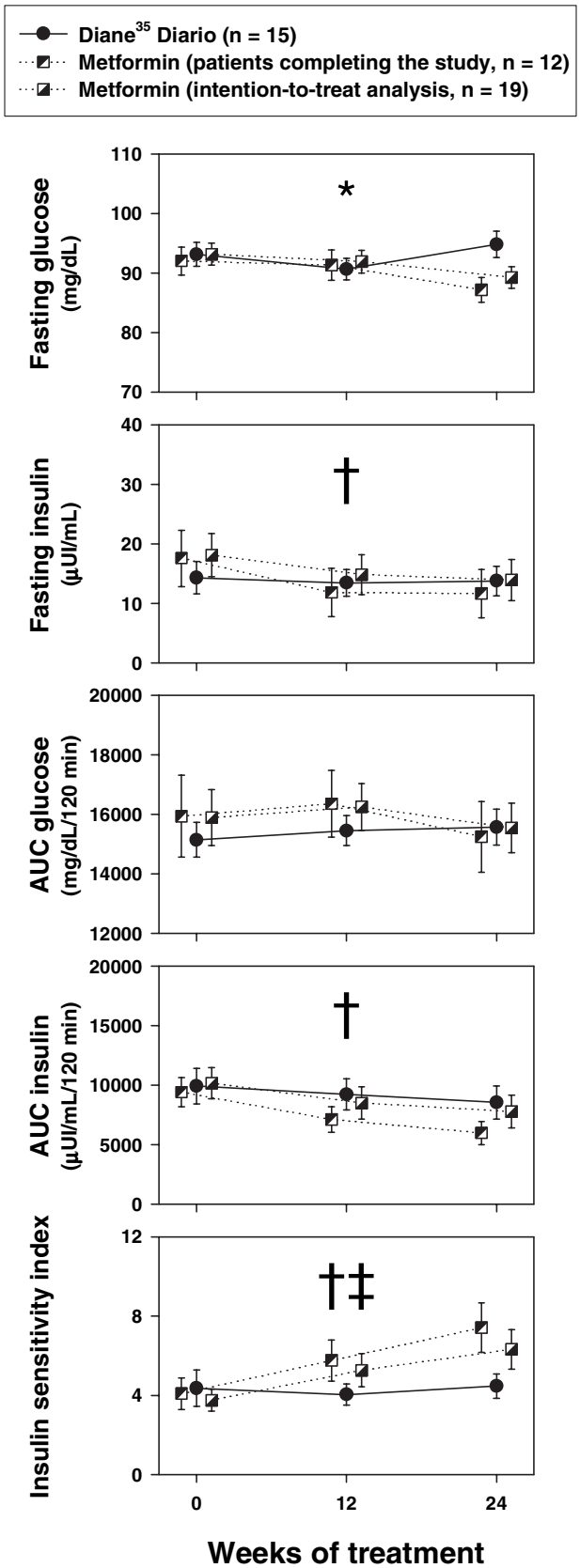

FIG. 4. Changes in indexes of glucose tolerance and insulin sensitivity in PCOS patients submitted to treatment with Diane[35] Diario or metformin for 24 wk. Data are means ± SEM. Because of the large dropout rate in the metformin arm, the figures show the analysis of the patients completing the study (n = 12) and also an intention-to-treat analysis including all the patients treated with metformin (n = 19), yet assuming for patients who did not complete the study that the dependent variables did not change at the missing visits with respect to the values observed in the previous visit. AUC, Area under the curve during the oGTT. *, $P < 0.05$ for the differences in the changes of each variable depending on the arm of treatment, in both analysis of patients who completed the study and in intention-to-treat analysis. †, $P < 0.05$ compared with baseline values in the whole group of patients, irrespective of the arm of treatment. ‡, $P < 0.05$ for the differences in the changes of each variable depending on the arm of treatment, only in patients completing the study but not by intention-to-treat analysis.

zyme that is remarkably sex steroid sensitive: estrogens decrease its activity, whereas androgens and androgenic progestins increase it (41). In conceptual agreement, and although certain oral contraceptives may worsen the lipid profile in the general population (42, 43), the amelioration of hyperandrogenism in PCOS women, combined with the antiandrogenic properties of cyproterone acetate and the estrogen component of Diane[35] Diario might overcome this undesirable effect, explaining its beneficial effect in PCOS patients (44).

Moreover, Diane[35] Diario had a minor impact on glucose tolerance because only a minimal increase in fasting glucose, which was not accompanied by a simultaneous increase in the AUC for plasma glucose during the oGTT, was observed between wk 12 and 24 of treatment. Furthermore, fasting insulin and the AUC for insulin during the oGTT decreased during treatment irrespective of the drug administered, and the frequencies of abnormalities in glucose tolerance did not change significantly during treatment with Diane[35] Diario. Therefore, our present results are in agreement with previous reports showing minor effects, if any, of Diane[35] Diario on glucose tolerance in PCOS patients (37, 39). Of note, the amelioration of insulin resistance observed during the 24 wk of our study in the patients treated with metformin was not accompanied by an actual reduction in the frequencies of abnormalities in glucose tolerance in these women.

Importantly, treatment with metformin was associated with a high dropout rate in our trial, in the range of the 38% (39) and 45% (40) of patients treated with this drug in previous clinical trials comparing Diane[35] Diario with metformin, respectively. Aside from the gastrointestinal side effects characteristic of metformin (45), which were directly related to the dropout of two of our patients, the usually suboptimal response of hirsutism with metformin (46) might have contributed to the loss of patients in our study considering that hirsutism is a frequent referral complaint in young PCOS patients such as ours (47). Nevertheless, the confirmation by intention-to-treat analysis of almost all the results obtained analyzing the patients who completed the study rules out a significant impact of the high dropout rate observed in the metformin arm of our trial. On the contrary, tolerance of Diane[35] Diario was excellent, and no patient dropped out of this arm of treatment.

However, our study is not free from limitations, especially the relatively short duration of treatment considering that PCOS is a chronic condition that requires long-term interventions. Yet also, it must be noted that our present results were obtained in a relatively small sample of PCOS patients

TABLE 2. Frequencies of disorders of glucose tolerance and dyslipidemia throughout the study

	Diane[35] Diario (n = 15)			Metformin					
				Patients completing the study (n = 12)			Intention-to-treat analysis (n = 19)		
	Baseline	12 wk	24 wk	Baseline	12 wk	24 wk	Baseline	12 wk	24 wk
Glucose tolerance									
Normal	10 (67)	12 (80)	8 (53)	10 (83)	9 (75)	10 (83)	14 (74)	14 (74)	15 (79)
Impaired fasting glucose	4 (27)	1 (7)	5 (33)	0 (0)	0 (0)	1 (8)	4 (21)	4 (21)	3 (16)
Impaired glucose tolerance	2 (13)	2 (13)	2 (13)	1 (8)	3 (25)	1 (8)	3 (16)	5 (26)	3 (16)
Type 2 diabetes	0 (0)	0 (0)	0 (0)	1 (8)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)
Global	5 (33)	3 (20)	7 (47)	2 (17)	3 (25)	2 (17)	5 (26)	5 (26)	4 (21)
Dyslipidemia									
Increased total cholesterol	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Increased LDL-cholesterol	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	1 (8)	1 (5)	1 (5)	2 (11)
Decreased HDL-cholesterol	8 (53)	4 (27)	4 (27)	4 (33)	6 (50)	4 (33)	9 (47)	11 (58)	9 (47)
Hypertriglyceridemia	2 (13)	1 (7)	2 (13)	1 (8)	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)
Global	8 (53)	5 (33)	4 (27)	4 (33)	6 (50)	4 (33)	9 (47)	11 (58)	9 (47)

Data are expressed as raw numbers (percent). There were no statistically significant differences in the frequencies of metabolic abnormalities between the arms of treatment, nor were there statistically significant changes in these frequencies during treatment when considering all patients as a whole, or each arm of treatment separately.

from Spain in whom overweight and obesity were frequent findings and who presented with the classic hyperandrogenic and oligoovulatory PCOS phenotype. Therefore any extrapolation of these results to PCOS patients of different race, ethnicity, and grade of obesity or presenting with different PCOS phenotypes should be made with prudence.

In summary, Diane[35] Diario and metformin are safe and effective single drugs for the treatment of PCOS. However, in unselected patients presenting with this disorder, Diane[35] Diario appears to be superior in terms of control of clinical and biochemical hyperandrogenism and restoration of menstrual regularity. Furthermore, this superior efficacy is not obtained at the expense of any clinically significant worsening in the metabolic cardiovascular risk profile of these women, yet, much on the contrary, use of Diane[35] Diario might even result in an increase in plasma Apo A-I and HDL-phospholipid levels that is not observed with metformin. Also, and although only metformin improved insulin resistance, this drug did not have a uniform beneficial impact on the disorders of glucose tolerance present in PCOS patients that could justify by itself its routine use in all PCOS cases.

We conclude that Diane[35] Diario and metformin should be considered for the treatment of PCOS patients, yet the choice for each drug requires careful consideration of the patient's clinical characteristics and preference. Furthermore, our present results stress that a putative deterioration of the metabolic cardiovascular risk profile of PCOS patients during administration of Diane[35] Diario is not supported by current scientific evidence and therefore should not be weighed against the use of this drug in any treatment decision making.

Acknowledgments

We thank Ms. Genoveva González from the Laboratory of the Department of Endocrinology of Hospital Ramón y Cajal for excellent technical help, and Ms. Francisca Cerrato from the Department of Biochemistry-Research for excellent help with the determination of the lipid profiles.

Received February 7, 2007. Accepted March 30, 2007.

Address all correspondence and requests for reprints to: Héctor F. Escobar-Morreale, M.D., Ph.D., Department of Endocrinology, Hospital Universitario Ramón y Cajal and Universidad de Alcalá, Carretera de Colmenar Viejo Km 9,1. 28034 Madrid, Spain. E-mail: hescobarm.hrc@salud.madrid.org.

This study was supported by the Spanish Ministry of Health and Consumer Affairs, Instituto de Investigación Carlos III Grants Fondo de Investigación Sanitaria PI050341 and PI050551 and Red de Diabetes y Enfermedades Metabólicas Asociadas (REDIMET) RD06/0015/0007; Ministry of Education and Science Grant SAF2005-07038; and by economic aid from Hospital Ramón y Cajal.

Present address for M.L.-R.: Department of Endocrinology, Hospital Universitario de La Princesa, Madrid, Spain.

Disclosure Information: All authors have nothing to declare.

References

1. **Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S, Escobar-Morreale HF** 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
2. **Diamanti-Kandarakis E, Christakou C** 2006 Prevalence, definition and clinical manifestations of polycystic ovary syndrome. Endocrinol Nutr 53(Suppl 1): 25–33
3. **Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, Janssen OE, Legro RS, Norman RJ, Taylor AE, Witchel SF** 2006 Position statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: An Androgen Excess Society guideline. J Clin Endocrinol Metab 91:4237–4245
4. **Escobar-Morreale HF, Luque-Ramírez M, San Millan JL** 2005 The molecular-genetic basis of functional hyperandrogenism and polycystic ovary syndrome. Endocr Rev 26:251–282
5. **Nelson VL, Qin K, Rosenfield RL, Wood JR, Penning TM, Legro RS, Strauss 3rd JF, McAllister JM** 2001 The biochemical basis for increased testosterone production in theca cells propagated from patients with polycystic ovary syndrome. J Clin Endocrinol Metab 86:5925–5933
6. **Gambineri A, Pasquali R** 2006 Insulin resistance, obesity and metabolic syndrome in polycystic ovary syndrome. Endocrinol Nutr 53(Suppl 1):49–55
7. **Alvarez-Blasco F, Botella-Carretero JI, San Millan JL, Escobar-Morreale HF** 2006 Prevalence and characteristics of the polycystic ovary syndrome in overweight and obese women. Arch Intern Med 166:2081–2086
8. **Dunaif A** 1997 Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 18:774–800
9. **Legro RS** 2003 Polycystic ovary syndrome and cardiovascular disease: a premature association? Endocr Rev 24:302–312
10. **Ehrmann DA, Cavaghan MK, Barnes RB, Imperial J, Rosenfield RL** 1999 Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 22:141–146
11. **Legro RS, Kunselman AR, Dodson WC, Dunaif A** 1999 Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 84:165–169

12. **Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS** 2006 A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update 12:673–683
13. **Lo JC, Feigenbaum SL, Escobar GJ, Yang J, Crites YM, Ferrara A** 2006 Increased prevalence of gestational diabetes mellitus among women with diagnosed polycystic ovary syndrome: a population-based study. Diabetes Care 29:1915–1917
14. **Rajkhowa M, Neary RH, Kumpatla P, Game FL, Jones PW, Obhrai MS, Clayton RN** 1997 Altered composition of high density lipoproteins in women with the polycystic ovary syndrome. J Clin Endocrinol Metab 82:3389–3394
15. **Berneis K, Rizzo M, Lazzaroni V, Fruzzetti F, Carmina E** 2007 Atherogenic lipoprotein phenotype and low-density lipoproteins size and subclasses in women with polycystic ovary syndrome. J Clin Endocrinol Metab 92:186–189
16. **Talbott E, Clerici A, Berga SL, Kuller L, Guzick D, Detre K, Daniels T, Engberg RA** 1998 Adverse lipid and coronary heart disease risk profiles in young women with polycystic ovary syndrome: results of a case-control study. J Clin Epidemiol 51:415–422
17. **Legro RS, Kunselman AR, Dunaif A** 2001 Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. Am J Med 111:607–613
18. **Lo JC, Feigenbaum SL, Yang J, Pressman AR, Selby JV, Go AS** 2006 Epidemiology and adverse cardiovascular risk profile of diagnosed polycystic ovary syndrome. J Clin Endocrinol Metab 91:1357–1363
19. **Apridonidze T, Essah PA, Iuorno MJ, Nestler JE** 2005 Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 90:1929–1935
20. **Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN** 2006 Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab 91:48–52
21. **Norman RJ, Davies MJ, Lord J, Moran LJ** 2002 The role of lifestyle modification in polycystic ovary syndrome. Trends Endocrinol Metab 13:251–257
22. **Ehrmann DA** 2005 Polycystic ovary syndrome. N Engl J Med 352:1223–1236
23. **Diamanti-Kandarakis E, Baillargeon J-P, Iuorno MJ, Jakubowicz DJ, Nestler JE** 2003 A modern medical quandary: polycystic ovary syndrome, insulin resistance, and oral contraceptive pills. J Clin Endocrinol Metab 88:1927–1932
24. **Costello M, Shrestha B, Eden J, Sjoblom P, Johnson N** 2007 Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome. Cochrane Database Syst Rev:CD005552
25. **Zawadzki JK, Dunaif A** 1992 Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine FP, Merriam GR, eds. Polycystic ovary syndrome. Boston: Blackwell Scientific Publications; 377–384
26. **Hatch R, Rosenfield RL, Kim MH, Tredway D** 1981 Hirsutism: implications, etiology, and management. Am J Obstet Gynecol 140:815–830
27. **Goodman A** 1999 Terminology and differential diagnosis of genital tract bleeding in women. In: Snyder PJ, Utiger RD, eds. Up to date in endocrinology and diabetes. Wellesley, MA: UpToDate, Inc.
28. **Escobar-Morreale HF, Serrano-Gotarredona J, Varela C, Garcia-Robles R, Sancho JM** 1997 Circulating leptin concentrations in women with hirsutism. Fertil Steril 68:898–906
29. **Escobar-Morreale HF, Lasunción MA, Sancho J** 2000 Treatment of hirsutism with ethinyl estradiol-desogestrel contraceptive pills has beneficial effects on the lipid profile and improves insulin sensitivity. Fertil Steril 74:816–819
30. **Vermeulen A, Verdonck L, Kaufman JM** 1999 A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 84:3666–3672
31. **Matsuda M, DeFronzo RA** 1999 Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 22:1462–1470
32. **Tai MM** 1994 A mathematical model for the determination of total area under glucose tolerance and other metabolic curves. Diabetes Care 17:152–154
33. **The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus** 2003 Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 26:3160–3167
34. **Friedewald WT, Levy RI, Fredrickson DS** 1972 Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18:499–502
35. **National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)** 2002 Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation 106:3143–3421
36. **Morin-Papunen LC, Vauhkonen I, Koivunen RM, Ruokonen A, Martikainen HK, Tapanainen JS** 2000 Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study. J Clin Endocrinol Metab 85:3161–3168
37. **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
38. **Gordon DJ, Rifkind BM** 1989 High-density lipoprotein–the clinical implications of recent studies. N Engl J Med 321:1311–1316
39. **Harborne L, Fleming R, Lyall H, Sattar N, Norman J** 2003 Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome. J Clin Endocrinol Metab 88:4116–4123
40. **Rautio K, Tapanainen JS, Ruokonen A, Morin-Papunen LC** 2005 Effects of metformin and ethinyl estradiol-cyproterone acetate on lipid levels in obese and non-obese women with polycystic ovary syndrome. Eur J Endocrinol 152:269–275
41. **Tikkanen MJ, Nikkila EA** 1987 Regulation of hepatic lipase and serum lipoproteins by sex steroids. Am Heart J 113:562–567
42. **Chasan-Taber L, Stampfer MJ** 1998 Epidemiology of oral contraceptives and cardiovascular disease. Ann Intern Med 128:467–477
43. **Baillargeon J-P, McCliah DK, Essah PA, Nestler JE** 2005 Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. J Clin Endocrinol Metab 90:3863–3870
44. **Villaseca P, Hormaza P, Cardenas I, Oestreicher E, Arteaga E** 2004 Ethinyl estradiol/cyproterone acetate in polycystic ovary syndrome: lipid and carbohydrate changes. Eur J Contracept Reprod Health Care 9:155–165
45. **Lord JM, Flight IH, Norman RJ** 2003 Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database Syst Rev:CD003053
46. **Harborne L, Fleming R, Lyall H, Norman J, Sattar N** 2003 Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome. Lancet 361:1894–1901
47. **Azziz R, Sánchez LA, Knochenhauer ES, Moran C, Lazenby J, Stephens KC, Taylor K, Boots LR** 2004 Androgen excess in women: experience with over 1000 consecutive patients. J Clin Endocrinol Metab 89:453–462

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.