Combined oral contraceptives plus spironolactone compared with metformin in women with polycystic ovary syndrome: a one-year randomized clinical trial

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Abstract

Objective: We aimed to compare a combined oral contraceptive (COC) plus the antiandrogen spironolactone with the insulin sensitizer metformin in women with polycystic ovary syndrome (PCOS).

Design: We conducted a randomized, parallel, open-label, clinical trial comparing COC (30 µg of ethinylestradiol and 150 µg of desogestrel) plus spironolactone (100 mg/day) with metformin (850 mg b.i.d.) for one year in women with PCOS (EudraCT2008–004531–38).

Methods: The composite primary outcome included efficacy (amelioration of hirsutism, androgen excess and menstrual dysfunction) and cardiometabolic safety (changes in the frequencies of disorders of glucose tolerance, dyslipidemia and hypertension). A complete anthropometric, biochemical, hormonal and metabolic evaluation was conducted every three months and data were submitted to intention-to-treat analyses.

Results: Twenty-four patients were assigned to COC plus spironolactone and 22 patients to metformin. Compared with metformin, COC plus spironolactone caused larger decreases in hirsutism score (mean difference 4.6 points, 95% CI: 2.6–6.7), total testosterone (1.1 nmol/L, 0.4–1.7), free testosterone (25 pmol/L, 12–39), androstenedione (5.5 nmol/L, 1.8–9.2) and dehydroepiandrosterone sulfate (2.7 µmol/L, 1.4–4.0). Menstrual dysfunction was less frequent with COC plus spironolactone (OR: 0.06, 95% CI: 0.02–0.23). No differences were found in frequencies of abnormal glucose tolerance (OR: 1.7, 95% CI: 0.7–4.4), dyslipidemia (OR: 0.6, 95% CI: 0.2–1.8) or hypertension (OR: 0.3, 95% CI: 0.5–2.0). No major adverse events occurred and biochemical markers were similarly safe with both treatments.

Conclusions: COC plus spironolactone was more effective than metformin for symptoms of PCOS showing similar safety and overall neutral effects on cardiometabolic risk factors.

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Introduction

Androgen excess is a major mechanism leading to polycystic ovary syndrome (PCOS) (1); yet, insulin resistance and obesity are frequently found in these women explaining the association of this syndrome with diabetes and increased cardiovascular risk factors (2). Accordingly, current strategies for the treatment of PCOS

include amelioration of androgen excess using combined oral contraceptives (COC) and/or antiandrogens and insulin sensitizers such as metformin (3).

COC remain the mainstay of the pharmacological therapy of PCOS (4). Although the practice of adding an antiandrogen to COC may be controversial (4, 5),

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antiandrogens such as spironolactone are clinically effective for treating hirsutism and may be beneficial for the dermatologic manifestations of PCOS in some cases (3). However, concerns about the metabolic and cardiovascular safety of COC explain the ongoing debate about the drug of choice for the long-term management of these women (6).

A very recent survey among European endocrinologists placed metformin as the treatment of choice for PCOS (7). Furthermore, a recent report of current practices in the United States showed that as many as 30.6% of women with PCOS received metformin without a medical claim for diabetes (8), even though current recommendations restrict the use of this drug to women with documented impaired glucose tolerance (5).

This occurred despite a Cochrane Review demonstrating the superior efficacy of COC over metformin and that the only advantages of the insulin sensitizer consisted of a reduction in fasting insulin and lower triglyceride levels (9). Similarly, our previous randomized clinical trial (RCT) comparing metformin with a COC containing cyproterone acetate as antiandrogenic progestin (10, 11, 12, 13, 14) confirmed the superior efficacy and overall metabolic and cardiovascular safety of the COC, with the notable exception of a mild increase in blood pressure that did not result into hypertension, however, in the women receiving this drug (15).

The increase in blood pressure during treatment with COC might be prevented, at least in theory, by the addition of spironolactone. This steroidal antiandrogen (16) and antihypertensive (17) drug is usually administered to hyperandrogenic women with PCOS in combination with a COC with the aim of preventing the frequent development of menstrual disturbances or even amenorrhea, and also to avoid feminization of a male fetus if unnoticed pregnancy occurs (18).

For the reasons outlined above, we have conducted a RCT comparing metformin with a combination of COC plus spironolactone for 1 year in women with PCOS, focusing on efficacy and safety in terms of cardiometabolic risk factors and adverse events.

Subjects and methods

Study design

We conducted a non-commercial, parallel, open-label RCT to compare treatments (<https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-004531-38/ES>). The study was approved by the local ethics committee and by the Spanish Agency of Medicines and Medical Devices.

Patients

We recruited women with PCOS reporting to our androgen excess outpatient clinic. We excluded patients seeking fertility and those with previous surgical treatment of PCOS or medical treatment with hormonal contraceptives, antiandrogens, insulin sensitizers or drugs that might interfere with blood pressure regulation, lipid profile or carbohydrate metabolism for the previous three months, history of serious illness including hypertension, diabetes mellitus, or cardiovascular events, pregnancy, contraindication for the use of metformin, COC or spironolactone and drug or alcohol abuse.

Diagnosis of PCOS required the presence of clinical and/or biochemical hyperandrogenism together with evidence of oligoovulation, provided that specific etiologies such as nonclassic 21-hydroxylase deficiency, hyperprolactinemia, hypothyroidism, Cushing's syndrome and androgen-secreting tumors had been excluded. Therefore, patients met all current definitions of PCOS (1, 19, 20) and showed the classic PCOS phenotype (19). Hirsutism was defined by a modified Ferriman–Gallwey score ≥ 8 points (21). Biochemical hyperandrogenism was defined by total testosterone ≥ 2.3 nmol/L, calculated free testosterone ≥ 35 pmol/L, androstendione ≥ 15.7 nmol/L and/or dehydroepiandrosterone sulfate ≥ 9.5 μ mol/L (22). Ovulatory dysfunction required the presence of menstrual dysfunction (menstrual cycle length: ≤ 26 or > 35 days) or evidence of luteal phase defect in women with normal menstrual cycles (day 20–24 serum progesterone concentrations: ≤ 12.7 pmol/L).

Written informed consent was obtained from all the participants or their legal representatives.

Randomization

We used stratified block randomization to allocate the patients to COC plus spironolactone or to metformin in a one-to-one ratio. Blocks of ten sealed opaque envelopes (five per arm of treatment) served for treatment assignment. Stratification for obesity, defined by a body mass index (BMI) ≥ 30 kg/m², was accomplished by using separate blocks for non-obese and for obese women. The aim of stratification for obesity was obtaining similar BMI and percentage of obese patients in both arms of treatment, but not estimating the possible impact of obesity on drug treatment. One investigator (H F E-M) generated the randomization envelopes, whereas another (M A) enrolled and assigned the participants to their arm of treatment. No masking method was used after randomization.

Procedures

Treatment was started on the first day of a spontaneous menstrual cycle or, in women with amenorrhea, after excluding pregnancy by proper testing. Drugs were administered using commercially available products. Metformin (Dianben, Merck, S.L., Mollet del Vallés, Spain) was started at a 425 mg b.i.d. during the first week of treatment with the aim of minimizing gastrointestinal side effects and maintained at an 850 mg dose b.i.d. thereafter. Women randomized to metformin were advised to use barrier contraception throughout the study. The COC plus spironolactone combination consisted of an oral contraceptive pill containing 30 µg of ethinylestradiol and 150 µg of desogestrel (Microdiol, Merck Sharp & Dohme de España, S.A. Madrid, Spain) and 100 mg/day of spironolactone (Aldactone, Pfizer, S.L., Alcobendas, Spain).

The choice of a COC containing desogestrel was based on its weak androgenic and glucocorticoid activities with the aim of minimizing any deleterious impact on metabolic variables (23). Moreover, according to our previous experience, use of this COC in women with hirsutism was associated with an improvement in insulin resistance and in the lipid profile (24). The COC was given for 21 days every 28 days and spironolactone was given every day. Drugs were continued for 12 months unless patients dropped out of the trial. Lifestyle changes were recommended at the initial visit, but no emphasis on these strategies was made during follow-up.

Two investigators (MA and FA-B) conducted the clinical, anthropometric and physical evaluations at baseline and after three, six, nine and 12 months of treatment. Variables recorded included hirsutism score, BMI, waist circumference and waist-to-hip ratio among others not reported here. 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). Blood samples were obtained five to ten days after a spontaneous menstrual bleeding or after excluding pregnancy in amenorrheic patients. After three days of a diet unrestricted in carbohydrates and a 12-h overnight fasting, basal samples were obtained for measurement of an androgenic profile consisting in serum total and free testosterone, androstenedione and DHEAS concentrations (22, 24). 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 and plasma were separated and frozen at -30°C until assayed.

The technical characteristics of the assays employed for plasma glucose, lipids and serum hormone measurements have been described elsewhere (22, 24). Homeostasis model assessment of insulin resistance (HOMA2-IR) were calculated according to Levy and coworkers (25). The composite insulin sensitivity index was calculated from the circulating glucose and insulin concentrations during the oGTT (26). 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 (27). We followed the guidelines of the Androgen Excess and PCOS Society to diagnose dyslipidemia (28).

Outcomes

The composite primary outcome included efficacy (amelioration of hirsutism, androgen excess and menstrual dysfunction) and cardiometabolic safety (changes in the frequencies of disorders of glucose tolerance, dyslipidemia and hypertension). Secondary outcomes included changes in anthropometric variables, office blood pressure, lipid profiles and indexes of glucose tolerance and insulin resistance. Regarding safety assessment, investigators were available at any time by telephone in case patients needed to report an adverse event. A serum biochemistry including ions and indexes of renal and hepatic function was obtained at every visit.

Statistical analysis

We used the online calculator of the Massachusetts General Hospital Biostatistics Center (http://hedwig.mgh.harvard.edu/sample_size/size.html) for sample size calculations. Regarding efficacy outcomes, calculations were based on the differences between the changes observed with COC or metformin in an earlier 6-month RCT from our group (10, 11). The s.d. of the differences in these changes were 3.3 points in the hirsutism score in favor of COC (10). Inclusion of 46 patients (group ratio 1:1) and 30 patients ending the trial would provide power above 80% to detect clinically relevant treatment differences in that clinical marker of androgen excess (≥ 3 points in hirsutism score), at a one-sided 0.05 significance level.

With respect to safety outcomes, we based the sample size calculations on the treatment differences in the changes observed in fasting glucose in the aforementioned RCT, which consisted of an increase with COC and a decrease with metformin (10). Considering that the s.d.

of the changes in fasting glucose was 0.5 mmol/L and the drop-out rate observed in this trial (10), we needed 44 patients to enter and 28 patients to complete the two-treatment parallel-design study in order to detect a clinically relevant treatment difference (0.6 mmol/L) in the changes in fasting glucose at a two-sided 0.05 significance level with 0.80 power.

Regarding main comparative analyses, data are shown as means $\pm$ s.d. or raw numbers (percentages) unless otherwise stated. We used Fisher's exact tests to analyze baseline differences in frequencies among the arms of treatment. The changes in the frequencies of metabolic disorders during the study were analyzed by univariate binary logistic generalized estimating equation models. For continuous variables, we assessed normality using the Kolmogorov–Smirnov test, and applied logarithmic transformation as needed to ensure normality. We compared the baseline characteristics of the patients randomized to receive COC plus spironolactone or metformin using unpaired *t* test. We submitted the data to a repeated-measures general linear model including the arm of treatment as the between-subjects effect and the visit (baseline, three, six, nine and 12 months) as the within-subjects effect. To evaluate the differences in the response to each treatment, we calculated the interaction between the between-subjects and within-subjects effects.

Because several patients discontinued treatment for different reasons, or missed intermediate visits, analyses of primary, secondary and safety outcomes were performed by intention to treat (ITT) including only participants who received at least one dose of study drug. ITT analysis assumed that the dependent variables had not changed at the missing visits with respect to the values observed in the previous visit.

Other than sample size calculations, analyses were performed using PASW Statistics 18 (SPSS) and STATA 13.1 (StataCorp). $P < 0.05$ was considered statistically significant.

Results

From March 2010 to March 2014, 549 consecutive women attended our androgen excess clinic for the first time, with 158 patients meeting the classic PCOS criteria. Of them, 46 patients, including 24 non-obese and 22 obese women, met inclusion criteria, did not show any exclusion criteria, and agreed to participate in the trial. Clinical and biochemical characteristics of the patients enrolled and not enrolled in the trial are summarized in [Supplementary Table 1](#) (see section on [supplementary data](#) given at the

end of this article). Women enrolled in the trial were more frequently obese than those not entering the trial, but no other relevant difference was found.

We did not observe baseline differences between the 24 patients randomized to COC plus spironolactone and the 22 patients allocated to metformin in age, anthropometrics, office blood pressure, clinical and biochemical indexes of androgen excess, lipid profiles and indexes of glucose tolerance or insulin resistance ([Table 1](#)).

Six patients in the COC plus spironolactone arm and nine patients on metformin dropped out before completing the study for several reasons ([Fig. 1](#)). Twelve patients, five in COC plus spironolactone and seven on metformin, were lost to follow-up ([Fig. 1](#)). Of the latter, one of the patients on metformin lost to follow-up after completing the nine-month visit had also missed the three-month appointment. Another patient in COC plus

Table 1 Baseline characteristics of the patients with PCOS randomized to treatment with a combined oral contraceptive pill (COC) plus spironolactone or with metformin. Data are means $\pm$ s.d. unless otherwise stated. Data were compared by unpaired *t*-tests or Fisher's exact test as appropriate. No statistically significant differences were found.

	COC plus spironolactone (n=24)	Metformin (n=22)
Age (years)	25 $\pm$ 5	23 $\pm$ 6
Menarche (years)	12 $\pm$ 2	12 $\pm$ 2
Body mass index (kg/m ²)	30.6 $\pm$ 7.9	31.2 $\pm$ 9.0
Waist (cm)	87 $\pm$ 16	88 $\pm$ 18
Waist-to-hip ratio	0.78 $\pm$ 0.08	0.78 $\pm$ 0.08
Systolic blood pressure (mmHg)	116 $\pm$ 11	118 $\pm$ 16
Diastolic blood pressure (mmHg)	73 $\pm$ 7	77 $\pm$ 11
Hirsutism score	10 $\pm$ 5	13 $\pm$ 7
Total testosterone (nmol/L)	2.6 $\pm$ 0.8	2.4 $\pm$ 0.8
Free testosterone (pmol/L)	44.9 $\pm$ 15.9	46.8 $\pm$ 23.5
Sex hormone-binding globulin (nmol/L)	41.4 $\pm$ 21.4	32.2 $\pm$ 15.7
Androstenedione (nmol/L)	13.8 $\pm$ 5.0	13.8 $\pm$ 6.4
Dehydroepiandrosterone sulfate (μ mol/L)	6.5 $\pm$ 2.4	7.2 $\pm$ 3.1
Estradiol (pmol/L)	184 $\pm$ 121	217 $\pm$ 224
Total cholesterol (mmol/L)	4.5 $\pm$ 1.0	4.5 $\pm$ 1.4
LDL cholesterol (mmol/L)	2.8 $\pm$ 0.8	2.7 $\pm$ 1.3
HDL cholesterol (mmol/L)	1.3 $\pm$ 0.4	1.3 $\pm$ 0.2
Triglycerides (mmol/L)	1.0 $\pm$ 0.5	1.0 $\pm$ 0.5
Fasting insulin (pmol/L)	89 $\pm$ 97	69 $\pm$ 51
Fasting glucose (mmol/L)	4.9 $\pm$ 0.4	4.9 $\pm$ 0.7
HOMA2-IR	1.6 $\pm$ 1.7	1.3 $\pm$ 0.9
Insulin sensitivity index	6.7 $\pm$ 5.1	7.0 $\pm$ 5.5

HDL, high-density lipoprotein; HOMA2-IR, homeostasis model assessment 2 of insulin resistance; LDL, low-density lipoprotein.

Figure 1
Flow diagram of the study.

spironolactone missed the nine-month appointment but completed all the other visits. Clinical and biochemical characteristics of the patients enrolled in the trial were similar compared with that of the subgroup of women who completed the study (Supplementary Table 1).

Primary composite outcome

The hirsutism score, serum total testosterone, free testosterone and androstenedione concentrations decreased more with COC plus spironolactone than with metformin (Fig. 2 and Table 2). Compared with pre-treatment values, COC plus spironolactone decreased hirsutism score by 68% (95% CI: 57–79) and serum concentrations of total testosterone by 54% (95% CI: 36–72), free testosterone by 79% (95% CI: 67–92), androstenedione by 46% (95% CI: 32–60) and DHEAS by 26% (95% CI: 15–37). On the contrary, women on metformin did not show any decrease in hirsutism score, total and free testosterone or androstenedione concentrations, and increased DHEAS levels by 35% (95% CI: 6–65).

Menstrual dysfunction persisted in women treated with metformin (13 of 19, 10 of 17, 10 of 14 and 8 of 13 patients after three, six, nine and 12 months of treatment respectively, $P=0.765$), whereas all the women treated with COC plus spironolactone had regular menses ($P=0.008$ by ITT analysis). Menstrual dysfunction was less frequent during treatment with COC plus spironolactone than with metformin (Table 3). We did not observe any change of difference between arms of treatment in the frequencies of

disorders of abnormal glucose tolerance, dyslipidemia or hypertension (Table 3 and Supplementary Table 2).

Secondary outcomes

When considered as a whole, patients lost weight and decreased their BMI regardless of the arm of treatment (Fig. 3). We did not observe any changes during the trial or differences between arms of treatment in waist circumference, waist-to-hip ratio, percentage of fat mass or systolic, mean and diastolic blood pressure (Fig. 3). Both serum HDL cholesterol and triglycerides concentrations increased with COC plus spironolactone, but not with metformin, whereas no changes or differences were observed in serum total and low-density lipoprotein cholesterol concentrations (Fig. 4). Fasting glucose levels decreased during the trial regardless of the arm of treatment, whereas no changes or differences were observed in fasting insulin concentrations, in HOMA2-IR values or in the insulin sensitivity index (Fig. 4).

Side effects

The side effects were generally mild and resulted in the drop-out of two patients on metformin because of mild but persistent gastrointestinal disturbances and one patient on COC plus spironolactone who developed a mild urticarial skin rash that resolved after stopping the medication. We did not observe changes during the trial or differences between arms of treatment in the mean values

Figure 2

Changes in clinical and biochemical indexes of androgen excess. Data are means $\pm$ S.E.M. of the patients remaining at each visit of the trial (figures under the x-axis) even though we conducted intention-to-treat statistical analyses. Data were submitted to a repeated-measures general linear model

of safety serum biochemical indexes with the exception of total alkaline phosphatase concentrations that decreased during the trial irrespective of the arm of treatment (data not shown). The frequencies of abnormal results in individual patients during the trial are summarized in [Supplementary Table 3](#). Such abnormal results were mild and did not result in the withdrawal from the trial in any case.

Discussion

In our present RCT, the combination of COC plus spironolactone was more effective than metformin for the treatment of PCOS in terms of amelioration of clinical and biochemical hyperandrogenism and restoration of regular menstrual bleeding. COC plus spironolactone induced a large decrease in the hirsutism score, normalized serum total and free testosterone and androstenedione concentrations and reduced serum DHEAS levels. All patients on COC plus spironolactone had regular menstrual bleeding. On the contrary, metformin did not improve any of the indexes of androgen excess and even increased serum DHEAS levels and did not improve menstrual irregularity in many patients.

The importance of these findings is that, even though COC and antiandrogens have been considered the drugs of choice for PCOS for many years (29), during the past two decades, insulin sensitizers, particularly metformin, have been proposed as an alternative treatment for this common condition (30). Compared with placebo, metformin and other insulin sensitizers improved androgen excess, menstrual regularity and ovulation rates in women with PCOS (31, 32, 33). But the strongest argument supporting the use of insulin sensitizers instead of COC for PCOS was that, considering that patients with this disorder present frequently with insulin resistance and its associated metabolic comorbidities, and because COC may worsen insulin resistance and glucose tolerance in the general population, these drugs should be replaced

including the visit as within-subjects effect and the arm of treatment as between-subjects effect. COC, combined oral contraceptive pill, DHEAS, dehydroepiandrosterone sulfate. *Statistically significant changes during the trial irrespective of the arm of treatment. †Statistically significant changes during the trial that were not the same in the women treated with COC plus spironolactone and in the women treated with metformin (interaction between visit evaluation and arm of treatment).

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Table 2 Differences between patients allocated to COC plus spironolactone compared with women allocated to metformin in the components (continuous variables) of the composite primary outcome. Continuous variables were submitted to univariate repeated-measures general linear models.

Continuous variables	Mean difference	95% confidence interval	Partial η^2	P value
Amelioration of androgen excess				
Decrease in hirsutism score (points)	4.6	2.6–6.7	0.257	<0.0001
Decrease in total testosterone (nmol/L)	1.1	0.4–1.7	0.191	<0.0001
Decrease in free testosterone (pmol/L)	25	12–39	0.256	0.0002
Decrease in androstenedione (nmol/L)	5.5	1.8–9.2	0.153	0.0002
Decrease in dehydroepiandrosterone-sulfate (μ mol/L)	2.7	1.4–4.0	0.195	<0.0001

by metabolically safe and effective insulin sensitizer drugs (6).

However, our present results provide evidence that when associated with lifestyle advice, COC plus spironolactone did not appear to influence negatively the metabolic milieu of PCOS, showing no overall differences with metformin on surrogate indexes of insulin resistance, lipid profiles, blood pressure and frequencies of metabolic disorders and hypertension. Moreover, the only changes observed in these indexes consisted of an increase in both high-density lipoprotein cholesterol and triglycerides concentrations with COC plus spironolactone that did not result in changes in the frequencies of patients with dyslipidemia during the trial. Furthermore, the safety profiles of both drugs were similarly good.

Hence, our study confirms and expands the findings of shorter trials conducted in the past. A 2007 Cochrane Review of four RCTs comparing metformin with COC did not find a higher metabolic risks with the latter (9). In two six-month trials published after the Cochrane Review cited above, an antiandrogenic COC increased blood pressure and arterial stiffness slightly, whereas metformin decreased or had a neutral effect on these variables (15, 34). Of note, these unfavorable changes were not observed in one of these studies when, as we have done in our present trial, a low-dose COC was combined with spironolactone (34). Moreover, the cardiometabolic and safety profiles of COC plus spironolactone and metformin were comparably good at least during the 1-year follow-up

period. In particular, our present results suggest that the addition of spironolactone to COC may also avoid the mild elevation in blood pressure associated with other COC in both healthy women and patients with PCOS (15), since spironolactone has both antiandrogen (16) and antihypertensive properties (17). Hence, concerns about a putative worsening in cardiovascular and metabolic variables with the use of COC should not limit the use of these drugs in women with the classic PCOS phenotype such as those included in our study, who are precisely those who associate the highest risk for these disorders (28).

However, our results should not be extrapolated to non-hyperandrogenic PCOS phenotypes. In a series of Danish patients with PCOS, half of whom presented with androgen concentrations within the normal range, metformin alone or in combination with the COC used here was superior to treatment with the COC alone regarding body composition and insulin resistance, the latter actually increasing during COC administration (35, 36). Since androgen excess may contribute directly to abdominal adiposity, adipose tissue dysfunction and insulin resistance in women with PCOS (2), we may speculate that amelioration of such mechanism in response to the antiandrogenic effects of spironolactone may account for the favorable outcomes of the insulin sensitivity indexes measured in our study. In agreement, in women with classic PCOS, the addition of spironolactone to COC prevented the increase in insulin levels during oGTT observed with COC alone in an earlier trial (34),

Table 3 Differences between patients allocated to COC plus spironolactone compared with women allocated to metformin in the components (dichotomous variables) of the composite primary outcome.

Dichotomous variables*	Odds ratio	95% confidence interval	z	P value
Frequency of menstrual dysfunction	0.06	0.02–0.23	–4.17	<0.0001
Frequency of cardiometabolic disorders				
Abnormal glucose tolerance	1.7	0.7–4.4	1.14	0.255
Dyslipidemia	0.6	0.2–1.8	–0.86	0.390
Hypertension	0.3	0.5–2.0	–1.23	0.219

Dichotomous variables were analyzed by univariate binary logistic generalized estimating equation models. *Dichotomous variables were coded as 0=absent and 1=present.

Figure 3

Changes in anthropometric variables and office blood pressure. Please refer to Fig. 2 for detailed explanations of the meaning of the symbols and statistics.

and the nonsteroidal antiandrogen flutamide has been shown to be superior to metformin in improving body composition and insulin sensitivity (37). In contrast, in women presenting with normoandrogenic phenotypes of PCOS, the deleterious effects of COC on insulin sensitivity may dominate the picture – as has been described in women from the general population (38) – explaining the findings in the Danish study described earlier (35, 36).

In our study, metformin did not improve symptoms of PCOS and was not superior to COC plus spironolactone in improving metabolic dysfunction, even though the number of patients completing treatment with this drug was small. While most evidence supports that metformin does not improve hirsutism (39) in agreement with our present results, metformin ameliorated the hyperandrogenemia and ovulatory dysfunction of PCOS in earlier proof-of-concept studies (31, 32) and short-term placebo-controlled trials (40). However, a recent meta-

Figure 4

Changes in lipid profile and indexes of insulin resistance. HDL, high-density lipoprotein; HOMA 2 IR, homeostasis model assessment 2 of insulin resistance; LDL, low-density lipoprotein. Please refer to Fig. 2 for detailed explanations of the meaning of the symbols and statistics.

analysis of these trials concluded that in patients with PCOS, and when associated with lifestyle modification, metformin induced no differences in anthropometric variables other than BMI (that decreased slightly), in surrogate markers of insulin resistance, fasting and area under the curve glucose, lipids and blood pressure, in clinical and biochemical hyperandrogenism, or in quality of life compared with placebo (41).

Among the limitations of our study we acknowledge: (i) the small sample size, which did not permit analyzing the impact of the presence or absence of obesity on the variables studied here; (ii) insulin sensitivity was assessed by HOMA2-IR and the composite insulin sensitivity index derived from the oGTT and these methods are relatively inaccurate when compared with euglycemic-hyperinsulinemic clamp techniques, particularly in small populations such as ours; (iii) even being among the

longest trials ever conducted in patients with PCOS, the one-year duration of our RCT precludes any conclusion about the possible long-term development of metabolic disorders in these women; (iv) carrying forward the last available observation in ITT analyses is a conservative single imputation method for a variable, which is expected to improve with an intervention, and this might not be the case for our pre-specified safety outcomes; and (v) since our design addressed menstrual regularity aiming actually at endometrial protection in patients not seeking fertility, we did not focus on confirming the recovery of ovulatory function in the subset of women allocated to metformin. These potential limitations may be compensated by advantages such as the inclusion of women suffering the most severe PCOS phenotype, the absence of commercial interests, and the fact that our limited research facilities mimic those available for routine clinical practice, highlighting the applicability of our present findings.

In summary, treatment with COC plus spironolactone was more effective than metformin for the clinical manifestations of classic PCOS, showing no disadvantages in terms of metabolic profiles. Hence, we suggest that COC plus spironolactone should be considered as a valid pharmacological approach for the treatment of patients with classic PCOS not seeking fertility.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-17-0516>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Clinical Study	M Alpañés, F Álvarez-Blasco and others	Randomized trial of common drugs for PCOS	177:5	408
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