0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(7):4068–4074

doi: 10.1210/jc.2005-0110

Prospective Parallel Randomized, Double-Blind, Double-Dummy Controlled Clinical Trial Comparing Clomiphene Citrate and Metformin as the First-Line Treatment for Ovulation Induction in Nonobese Anovulatory Women with Polycystic Ovary Syndrome

Stefano Palomba, Francesco Orio, Jr., Angela Falbo, Francesco Manguso, Tiziana Russo, Teresa Cascella, Achille Tolino, Enrico Carmina, Annamaria Colao, and Fulvio Zullo

Department of Obstetrics and Gynecology (S.P., A.F., T.R., F.Z.), University "Magna Graecia" of Catanzaro, 80131 Naples, Italy; Departments of Molecular and Clinical Endocrinology and Oncology (F.O., T.C., A.C.), Internal Medicine (F.M.), and Obstetrics and Gynecology (A.T.), University "Federico II" of Naples, 80138 Naples, Italy; and Department of Endocrinology (E.C.), University of Palermo, 90128 Palermo, Italy

Context: Although metformin has been shown to be effective in the treatment of anovulation in women with polycystic ovary syndrome (PCOS), clomiphene citrate (CC) is still considered to be the first-line drug to induce ovulation in these patients.

Objective: The goal of this study was to compare the effectiveness of metformin and CC administration as a first-line treatment in anovulatory women with PCOS.

Design: We describe a prospective parallel randomized, double-blind, double-dummy controlled clinical trial.

Setting: The study was conducted at the University "Magna Graecia" of Catanzaro, Catanzaro, Italy.

Patients: One hundred nonobese primary infertile anovulatory women with PCOS participated.

Interventions: We administered metformin cloridrate (850 mg twice daily) plus placebo (group A) or placebo plus CC (150 mg for 5 d from the third day of a progesterone withdrawal bleeding) (group B) for 6 months each.

Mean outcome measures: The main outcome measures were ovulation, pregnancy, abortion, and live-birth rates.

Results: The subjects of groups A (n = 45) and B (n = 47) were studied for a total of 205 and 221 cycles, respectively. The ovulation rate was not statistically different between either treatment group (62.9 *vs.* 67.0%, $P = 0.38$), whereas the pregnancy rate was significantly higher in group A than group B (15.1 *vs.* 7.2%, $P = 0.009$). The difference found between groups A and B regarding the abortion rate was significant (9.7 *vs.* 37.5%, $P = 0.045$), whereas a positive trend was observed for the live-birth rate (83.9 *vs.* 56.3%, $P = 0.07$). The cumulative pregnancy rate was significantly higher in group A than group B (68.9 *vs.* 34.0%, $P < 0.001$).

Conclusions: Six-month metformin administration is significantly more effective than six-cycle CC treatment in improving fertility in anovulatory nonobese PCOS women. **(*J Clin Endocrinol Metab* 90: 4068–4074, 2005)**

POLYCYSTIC OVARY SYNDROME (PCOS) is one of the most common reproductive endocrinopathies, affecting approximately 5–10% of women of reproductive age (1). Although various criteria have been proposed for the diagnosis of PCOS (2, 3), oligoanovulation due to ovarian dysfunction continues to be the pivotal feature that makes this syndrome the major cause of anovulatory infertility in developed countries (4).

In fact, some approaches have been proposed to induce the ovulation in women with PCOS (5).

First Published Online April 19, 2005

Abbreviations: AE, Adverse experience; AUC, area under the curve; BMI, body mass index; CC, clomiphene citrate; NNT, number needed to treat; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; TV-USG, transvaginal ultrasonography; WHR, waist to hip ratio.

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

Clomiphene citrate (CC) was the first agent used in experiments for ovulation induction in oligomenorrheic women by Holtkamp *et al.* (6). It was then introduced into general clinical practice by Greenblatt (7, 8). For many years it represented the first therapeutic option managing anovulatory infertility (5). CC acts by various mechanisms; its action can be explained with double-estrogenic and antiestrogenic activity (9). Mainly CC exerts an antiestrogenic action, thereby increasing the pulse frequency and concentration of the FSH and LH, with an increase of ovarian follicles reaching ovulation (9).

The treatment with CC in anovulatory PCOS women is related to an ovulation rate of 60–85% and a pregnancy rate of 30–40% (10). The exact explanation for the discrepancy between ovulation and pregnancy rates is unknown, but several possible hypotheses have been suggested (11). Today CC is routinely used by many endocrinologists and gynecologists to treat infertile anovulatory PCOS patients due to

the low costs, the limited dose-dependent side effects, and the simplicity of administration and management (no need for ongoing monitoring) (5).

Metformin cloridrate, an oral biguanide for type 2 diabetes mellitus, is a safe and effective drug that is recently used for the treatment of PCOS patients (12–15). The administration of metformin improves clinical and biochemical features of PCOS and induces ovulatory cycles in anovulatory CC-resistant or nonresistant patients with PCOS (12–15). It also improves the ovulation rate as an additional treatment in women who received CC (12–15). Systematic reviews (13–15) have confirmed the efficacy of metformin for the treatment of anovulatory infertile PCOS patients, whereas in terms of pregnancy rate, there are few data in literature regarding the effectiveness of metformin. Nevertheless, a significant advantage in all reproductive outcomes has been more recently observed after metformin administration when compared with laparoscopic ovarian diathermy as the second step for the management of anovulation in CC-resistant PCOS women (16).

Despite the fact that the use of metformin has been suggested as the first-line treatment to induce ovulation in patients with PCOS (17), until now no head-to-head study comparing CC with metformin has been performed. Based on these considerations, the aim of the present trial was to compare the efficacy of metformin to CC as the first-line treatment for the anovulatory infertility in nonobese women with PCOS in a randomized, double-blind, double-dummy, controlled fashion.

Patients and Methods

Patients

Between April 2003 and September 2003, a total of 100 nonobese primary infertile anovulatory women with PCOS were enrolled.

The diagnosis of PCOS was made according to the National Institutes of Health criteria (2). The exclusion criteria for all subjects included: age younger than 20 or older than 34 yr; body mass index (BMI) higher than 30 kg/m^2 (18); neoplastic, metabolic (including glucose intolerance), hepatic, and cardiovascular disorders or other concurrent medical illnesses; hypothyroidism, hyperprolactinemia, Cushing's syndrome, and nonclassical congenital adrenal hyperplasia as excluded by appropriate tests; and current or previous (within the last 6 months) use of oral contraceptives, glucocorticoids, antiandrogens, ovulation induction agents, antidiabetic and antiobesity drugs, or other hormonal drugs. Other exclusion criteria were as follows: no uterine bleeding after progesterone challenge test (100 mg natural progesterone im; Prontogest, Amsa, Rome, Italy); organic pelvic diseases; previous pelvic surgery; suspected peritoneal factor infertility; and tubal or male factor infertility. The tubal and male factors of infertility were excluded with a hysterosalpingogram and semen analysis, respectively. We also excluded women who intended to start a diet or specific program of physical activity. All subjects had a normal physical activity, and none drank alcoholic beverages.

Protocol and treatment

The procedures used were in accordance with the guidelines of the Helsinki Declaration on human experimentation. The study was approved by the Institutional Review Board of the University "Magna Graecia" of Catanzaro. The purpose of the protocol was carefully explained to all the women, and written consent was obtained before beginning the study.

At study entry, all subjects underwent venous blood drawing to evaluate the complete hormonal assays, serum glucose, and insulin levels. All blood samples were obtained in the morning between 0800 and 0900 h after a 3-d, 300-g carbohydrate diet and 12-h overnight fasting and resting in bed during the early proliferative phase (second to third day) of the progesterone-induced withdrawal uterine bleeding (100 mg natural progesterone im). Blood samples (5 ml) were collected in tubes containing EDTA after a 30-min resting period in the supine position. The samples were immediately centrifuged at 4 C for 20 min at 1600 × *g*, and plasma samples were stored at −20 C. Plasma hormone concentrations were measured by specific RIA as previously reported (19). SHBG levels were measured also using an immunoradiometric assay (19). Serum insulin was measured by a solid-phase chemiluminescent enzyme immunoassay using commercially available kits. Blood glucose levels were determined by the glucose oxidase method (19).

For each subject the homeostasis model of assessment [fasting glucose (millimoles per liter) × fasting insulin (microunits per milliliter)/22.5], the fasting glucose to insulin ratio (milligrams per 10^{-4} units), and the free androgen index [testosterone (nanomoles per liter)/SHBG × 100]) were calculated.

Glucose and insulin values were also detected after the oral glucose tolerance test (OGTT). Glucose and insulin concentrations were specifically measured 30 min after the insertion of an iv catheter to detect the fasting levels (time 0) before OGTT. Afterward, each subject orally received a load of 75 g glucose. Further blood samples (10 ml each) were obtained at 30-min intervals for the following 2 h during the infusion period (times 30, 60, 90, and 120), and glucose and insulin concentrations were determined. Glucose intolerance was assessed by World Health Organization criteria (20). For each patient the area under curve (AUC) and the $AUC_{glucose}$ to $AUC_{insulin}$ ratio were calculated (21).

At baseline in each patient, the same operator calculated the modified Ferriman-Gallwey score (22); evaluated the patients' daily physical activity, job, and daily activities using a semiquantitative questionnaire (23); performed a transvaginal ultrasonography (TV-USG); and assessed the anthropometric measurements. The anthropometric measurements included height, weight, BMI and waist to hip ratio (WHR). Body height and weight were measured without shoes and clothes, respectively. BMI was measured as the ratio between the weight and the square of the height (kilograms per square meter). WHR was calculated as the ratio between the smallest circumference of torso (between the 12th rib and the iliac crest) and the circumference of the hip (considered as the maximal extension of the buttocks). WHR was calculated with the patients in standing position with relaxed abdomen, arms at sides, and joined feet.

The subjects were then randomly allocated into two treatment groups of 50 women each (groups A and B). The randomization was carried out using an online software (www.randomization.it) to generate a random allocation sequence in double block as method of restriction. The random allocation sequence was concealed until the interventions were assigned. Group A was treated with metformin cloridrate (Metforal, Laboratori Guidotti, Pisa, Italy) at a dosage of 850 mg twice daily plus placebo tablets (three tablets daily for 5 d starting from the third day of a progesterone-induced withdrawal bleeding; 10 mg natural progesterone im), whereas group B received placebo tablets (two tablets daily) plus CC (Serophene, Serono, Rome, Italy) at a dosage of 150 mg (three tablets) for 5 d starting from the third day of a progesterone-induced withdrawal bleeding. The placebo consisted of polyvitamins tablets similar in appearance to metformin and/or CC. The patients were instructed to take the tablets with their meals. The drug and the placebo were packaged in the pharmacy of the University of Catanzaro and labeled according to subject number. The duration of treatment was 6 months. For the overall study period, operators and patients were blind to the treatment allocation.

After 6 months of treatment, women who did not achieve ovulation in groups A and B were administered CC and metformin, respectively, at the same doses and regimens as described above (cross-over). PCOS women having ovulatory cycles who did not achieve a pregnancy were treated with three trials of controlled ovarian stimulation followed by intrauterine insemination before assisted reproductive techniques (10–12).

Throughout the study, no change in diet and physical activity was implemented. On the contrary, the subjects were instructed to follow their usual diet and physical activity. Patients who became pregnant throughout the study suspended the treatments.

Each patient underwent serial TV-USG measurements by the same experienced operator using an ultrasonic scanner (Aplio, Toshiba Medical Systems, Rome, Italy) equipped with a 7.5-MHz vaginal probe. Scans

were performed every 3 d beginning on the seventh day after treatment starting (for the first cycle) and after the onset of menses. When the follicular dimensions (arithmetic mean of the two main diameters of the follicle) achieved at least 16 mm, the TV-USG was performed daily. When the follicle dimensions yielded at least a mean diameter of 18 mm, each woman was asked to have intercourse four times every 2 d. No agent to induce ovulation, *e.g.* human chorionic gonadotropin, was administered throughout the study.

During the study, the ovulation, pregnancy, abortion, and live-birth rates were evaluated in each woman. The ovulation was retrospectively defined with the observation of a decrease in follicular dimensions and liquid in the cul-de-sac and confirmed by plasma P assay greater than 10 ng/ml (SI 32 nmol/liter). Anovulatory women received a further dose of 100 mg natural progesterone im, in the absence of spontaneous withdrawal bleeding after 40 d from last progesterone-induced uterine bleeding.

Ovulation rate was calculated as the percentage of ovulatory cycles per total cycles. The pregnancy rate was defined as the percentage of pregnancies per total cycles. A rising β-human chorionic gonadotropin and the sonographic evidence of intrauterine gestational sac were considered criteria to define a pregnancy. The abortion rate was defined as a percentage of miscarriage during the first 12 wk of gestation per total pregnancies. The live-birth rate was obtained after a 9-month extension of the follow-up period and was defined as a percentage of women with baby alive per women who achieve a pregnancy.

Subjects were instructed to report the characteristics of their menstrual cycle and the onset of any adverse experiences (AEs) in a daily diary. The length and frequency (percentage of observed menses per number of expected menses) of the menstrual bleedings were evaluated. The quantity of the cyclical uterine bleedings was also evaluated subjectively by each woman using a rank analog scale ranging from 1 to 10. A value of 0 was given arbitrarily in the absence of menses; a value of 5 was given for uterine bleedings defined as normal and a value of 10 for uterine bleeding defined as severe. For each AE reported in the daily diary, the severity, duration, and a possible cause-effect relationship with drug administrations was noted. To evaluate the compliance with the treatment and protocol, the number of skipped tablets, the changes in diet, physical activity, and weight as well as the timing of the intercourses were also recorded in the same diary.

Standard clinical evaluations and laboratory analysis, including hematological, renal function and liver function tests, and microscopic examinations of sediment from midstream urine specimens were performed at study entry and after 6 months of treatment.

Statistical analysis

Considering that our study population was made up of infertile patients, the primary end point of our trial was the pregnancy rate. From the literature we estimated that the expectant cumulative pregnancy rate after control treatment (CC administration) ranged between 30 and 40% (10), and after experimental treatment (metformin administration) was approximately 70% (16). The sample size calculation was based on the hypothesis that after treatment, 40% of patients in the control group would be pregnant, compared with 70% in the experimental group. This computation assumes that the difference in proportions is -0.30 (specifically, 0.40 *vs.* 0.70). This effect was selected as the smallest effect that it would be important to detect, in the sense that any smaller effect would not be of clinical or substantive significance. It is also assumed that this effect size is reasonable, in the sense that an effect of this magnitude could be anticipated in this field of research. With a two-tailed test of alpha = 0.05 and beta = 0.20, two groups of 42 patients each were required to yield a statistically significant result. To allow an unpredictable number of withdrawals, we decided to enroll a total of 100 patients in the expectation that at least 42 patients would be left in each group.

Data were expressed as mean ± SD and analyzed by using the intention-to-treat method. The Kolmogorov-Smirnov statistic with a Lilliefors significance level was used for testing normality, and the unpaired t test and the Mann-Whitney U test were applied appropriately. For categorical variables, the Pearson χ^2 test was performed; conversely the Fisher's exact test was required for the frequency tables when more than 20% of the expected values were less than 5. $P \leq 0.05$ or less was considered significant. The Statistics Package for Social Science (SPSS 13.0; SPSS Inc., Chicago, IL) was used for statistical analyses. The number needed to treat (NNT) was calculated with StatsDirect (release 2.4.3, Cheshire, UK).

Results

An overview of the trial is shown in Fig. 1. The numbers of withdrawals were similar in the two groups (five and three women in groups A and B, respectively). Four patients (three and one in groups A and B, respectively) were specifically excluded because they missed their first follow-up visit. One woman from each group was excluded in the final analysis due to lack of compliance with the treatment (they did not assume tablets during the first 3 wk for drug-related AEs).

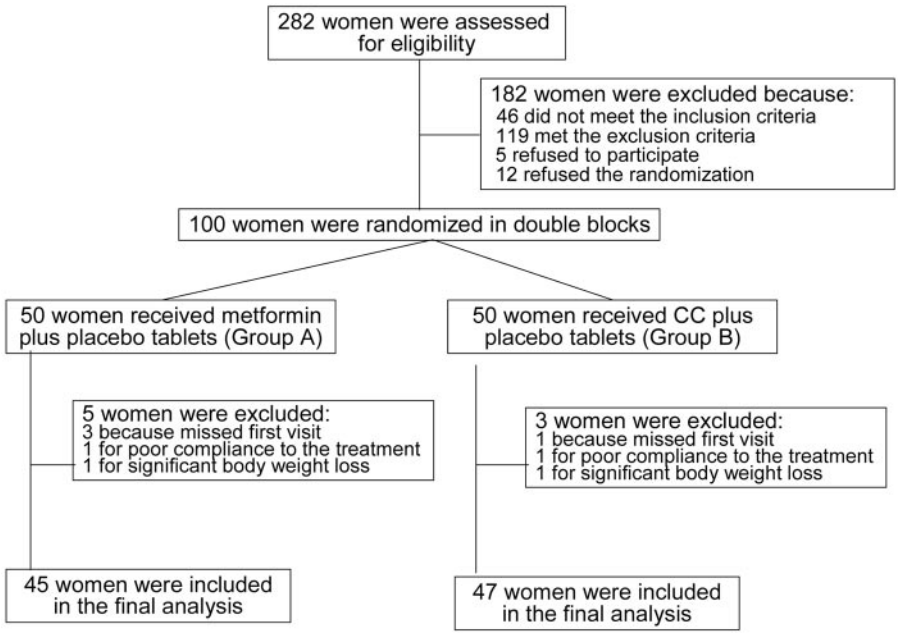

FIG. 1. An overview of the trial.

Finally, one woman in each group was excluded because of a reduction in body weight (>5% from basal value) was observed after the first 3 months of the study (Fig. 1).

The patients' characteristics are presented in Table 1. After randomization, no difference was detected in any clinical, hormonal, and metabolic parameter between the treatment groups (Table 1). The two groups were similar for the percentage of normal-weight (BMI ± SD; 22.3 ± 2.0 *vs.* 22.6 ± 2.1 kg/m^2 for groups A and B, respectively) and overweight (BMI ± SD; 28.3 ± 1.2 *vs.* 28.2 ± 1.3 kg/m^2 for groups A and B, respectively) PCOS women. No woman in either group was lean.

At study entry, all women had polycystic ovaries at TV-USG examination

TABLE 1. Clinical, hormonal, and metabolic data of anovulatory PCOS women after randomization

Treatment	Group A metformin plus placebo	Group B clomiphene plus placebo	*P*
Age (yr)	26.4 ± 2.9	25.9 ± 2.7	0.37
BMI (kg/m^2)	27.0 ± 2.9	26.7 ± 2.8	0.60
Overweight patients [n (%)]	39/50 (78)	38/50 (76)	0.81
Normal-weight patients [n (%)]	11/50 (22)	12/50 (24)	
WHR	0.87 ± 0.5	0.86 ± 0.4	0.91
Duration of infertility (months)	19.2 ± 4.6	20.3 ± 4.1	0.21
Modified Ferriman-Gallwey score	15.8 ± 3.0	15.2 ± 2.8	0.30
Physical activity score[a]	1.7 ± 0.4	1.8 ± 0.5	0.27
Cigarettes smoked (n/d)	4.3 ± 4.1	5.2 ± 3.7	0.25
FSH (mIU/ml)	7.6 ± 1.9	8.1 ± 2.1	0.67
LH (mIU/ml)	17.8 ± 4.9	19.0 ± 5.1	0.23
TSH (μU/ml)	2.7 ± 0.5	2.6 ± 0.6	0.37
PRL (ng/ml)	8.9 ± 2.6	9.7 ± 2.7	0.13
E_2 (pg/ml)	36.9 ± 9.7	34.0 ± 8.3	0.11
P (ng/ml)	0.7 ± 0.5	0.6 ± 0.4	0.27
17-OHP (μg/liter)	1.7 ± 0.4	1.8 ± 0.6	0.33
T (ng/ml)	0.9 ± 0.3	1.0 ± 0.3	0.10
A (ng/ml)	1.6 ± 0.3	1.7 ± 0.2	0.05
DHEAS (ng/ml)	2,649 ± 386	2,704 ± 452	0.51
SHBG (nmol/liter)	26.7 ± 6.4	27.2 ± 7.2	0.71
FAI (%)	12.6 ± 6.3	13.7 ± 6.5	0.39
Fasting glucose (mg/dl)	78.9 ± 10.3	82.7 ± 10.1	0.07
Fasting insulin (μU/ml)	19.5 ± 5.4	20.4 ± 5.6	0.42
GIR ($mg/10^{-4}$ U)	4.1 ± 1.3	4.2 ± 1.4	0.71
HOMA	3.8 ± 1.6	4.2 ± 1.2	0.16
OGTT			
$AUC_{glucose}$ (mg/dl per 120 min)	15,797 ± 5,342	16,893 ± 4,665	0.27
$AUC_{insulin}$ (μU/ml per 120 min)	16,976 ± 4,576	18,143 ± 5,679	0.26
$AUC_{glucose}$ to $AUC_{insulin}$ ratio	1.3 ± 0.7	1.4 ± 0.7	0.28

Data are expressed as mean ± SD. PRL, Prolactin; E_2, 17β-estradiol; P, progesterone; 17-OHP, 17-hydroxy progesterone; T, testosterone; A, androstenedione; DHEAS, dehydroepiandrosterone sulfate; FAI, free androgen index; GIR, glucose to insulin ratio; HOMA, homeostasis model of assessment. The biochemical assays are reported in metric units. Conversion factor for SI: A, 3492 (nanomoles per liter); DHEAS, 0.002714 (micromoles per liter); F_2, 3.671 (picomoles per liter); FSH, 1.0 (international units per liter); fasting glucose, 0.05551 (nanomoles per liter); fasting insulin (7.175 picomoles per liter); LH, 1.0 (international units per liter); 17-OHP, 3.026 (nanomoles per liter); P, 3.180 (nanomoles per liter); PRL, 1.0 (micrograms per liter); T, 3.467 (nanomoles per liter); TSH, 1.0 (milliunits per liter).

[a] 1, Low; 2, moderate; 3, high.

Results included in the present study were obtained from a total of 92 patients; 45 and 47 subjects in groups A and B, respectively. The subjects of groups A and B were studied for a total of 205 and 221 cycles, respectively. Considering the sample size included in the final analysis (Fig. 1), the data obtained (as below detailed) had a poststudy power greater than 95% for the primary end point (cumulative pregnancy rate).

Table 2 shows the ovulation and pregnancy rates for each month of treatment in both groups. The cumulative ovulation rate over the 6-month period was not statistically different between both treatment groups [62.9 (129 of 205) *vs.* 67.0% (148 of 221) in groups A and B, respectively; $P = 0.38$], whereas the pregnancy rate per ovulatory cycle resulted significantly higher in group A in comparison with group B [15.1 (31 of 205) *vs.* 7.2% (16 of 221) in groups A and B, respectively; $P = 0.009$]. The resulting differences in the abortion rate found between the groups were significant [9.7 (three of 31) *vs.* 37.5% (six of 16) in groups A and B, respectively; $P = 0.045$], whereas a positive trend was observed for the live-birth rate [83.9 (26 of 31) *vs.* 56.3% (nine of 16) in groups A and B, respectively; $P = 0.07$].

None of the women had multiple pregnancies in either group

Twenty-eight patients with ongoing pregnancies for group A and 10 for group B were checked during the 9-month follow-up extension. In group A, there was a premature rupture of membranes at 28 wk of gestation with a following neonatal death and an intrauterine fetal death at 32 wk of gestation for unexplained causes. In group B, there was a massive abruptio placentae with acute fetal distress and then fetal death at 36 wk of gestation. One case of pregnancy-induced hypertension was observed in group A, whereas two cases of glucose intolerance were detected in group B. The delivery was vaginal in 73.1% (19 of 26) and 77.8% (seven of nine) pregnancies for group A and B, respectively. In the other cases, a cesarean section was performed due to various causes, whereas no vacuum extractor or forceps were used in any case. The Apgar score at 5 and 10 min did not differ between the two groups. No malformation was detected in both groups.

After 6 months of treatment, a significant difference was observed in the cumulative pregnancy rate [68.9% (31 of 45) *vs.* 34.0% (16 of 47) for groups A and B, respectively; $P < 0.001$]. Considering the pregnancy as a treatment-related event, the NNT was of three benefits (two to seven benefits; 95% confidence interval).

At the end of the 6-month treatment, 6.7% (three of 45) and 34.0% (16 of 47) PCOS women in groups A and B, respectively, were still oligo- or amenorrheic ($P = 0.02$), whereas 24.4% (11 of 45) and 31.9% (15 of 47) PCOS women in groups A and B, respectively, having ovulated (as detected by serial TV-USG assessments and P assay), did not become pregnant ($P = 0.43$).

Throughout the study, the length, quantity, and frequency of uterine bleedings did not differ between the two treatment groups (data not shown).

During the study, the two treatment schedules were generally well tolerated, and the total incidence of all AEs was not significantly different between the two groups. No se-

TABLE 2. Ovulation and pregnancy rates in PCOS women treated with metformin cloridrate (group A) or CC (group B) during each cycle of treatment

Cycle	Ovulation rate [no. ovulatory cycles/no. cycles (%)]			Pregnancy rate [no. pregnancies/no. cycles (%)]		
	Group A	Group B	*P*	Group A	Group B	*P*[a]
1	19/45 (42.2)	39/47 (83.0)	<0.001	3/45 (6.7)	6/47 (12.8)	0.49
2	24/42 (57.1)	33/41 (80.5)	0.02	4/42 (9.5)	5/41 (12.2)	0.74
3	25/38 (65.8)	25/36 (69.4)	0.74	6/38 (15.8)	2/36 (5.6)	0.26
4	22/32 (68.8)	19/34 (55.9)	0.28	5/32 (15.6)	2/34 (5.9)	0.25
5	21/27 (77.8)	17/32 (53.1)	0.049	6/27 (22.2)	1/32 (3.1)	0.04
6	18/21 (85.7)	15/31 (48.4)	0.006	7/21 (33.3)	0/31 (0.0)	0.001

Data were analyzed using χ^2 test unless otherwise specified.
[a] Fisher's exact test.

rious AE or laboratory abnormalities were reported in either group during the study. The distribution of drug-related AEs was also not significantly different between the two groups [22.2% (10 of 45) *vs.* 19.1% (nine of 47) for groups A and B, respectively; $P = 0.72$]. The drug-related AEs specifically consisted of diarrhea, flatulence, and nausea during metformin administration, whereas headache, hot flushes, and nervousness were present during CC administration. As reported before, one case for each group stopped the treatment for drug-related AEs.

Discussion

The goal for the treatment of anovulatory infertility is the induction of monoovulatory cycles (24). The use of gonadotropins for the ovulation induction in anovulatory PCOS women has been extensively studied, showing a high success rate (25). Furthermore, during gonadotropin administration, there is a need for an experienced operator and careful sonographic and biochemical monitoring to avoid or reduce the risk of ovarian hyperstimulation and multiple pregnancies, particularly higher in PCOS patients due to frequent multifollicular growth. Moreover, the treatment with gonadotropins requires a relevant investment of time and money. For these reasons, several treatments have been proposed to induce the monoovulation in women with PCOS before gonadotropin use (4, 5). Nevertheless, because CC has been introduced for ovulation induction (7, 8), until now no treatment has displaced this drug as a first therapeutic option in the management of anovulatory infertility (4, 5).

Our data confirm that not only is CC administration related with a high rate of ovulations (16) in PCOS patients but also that a percentage of subjects remains anovulatory after CC treatment or, having ovulated with CC, does not become pregnant (16). In fact, in the present study, the ovulation rate after CC use was 67%, whereas the pregnancy rate was only approximately 37%. Many mechanisms have been proposed to explain this figure, such as the antiestrogenic effects on the endometrium, cervical mucus, uterine blood flow, the influences on tubal transport and oocyte quality and maturity, and the increased risk in subclinical pregnancy loss (5, 11).

In 1994 Velazquez *et al.* (26) first showed that a drug with insulin-sensitizing action (*i.e.* metformin cloridrate) was effective in PCOS patients in improving the hormonal and metabolic pattern and facilitating normal menstrual cycles and pregnancy. Both observational (12) and randomized, controlled trials (13–15) have successively confirmed the effectiveness of metformin in PCOS women in terms of menstrual cyclicity and/or ovulation. Metformin has shown to be effective in PCOS, increasing the ovulation rate in patients later treated with CC and improving the response to CC in CC-resistant patients with PCOS (12–15). Finally, we have recently demonstrated that metformin is more cost-effective than laparoscopic ovarian diathermy as a second-step procedure in treating overweight CC-resistant PCOS women (16).

Our findings confirm that metformin is effective in inducing ovulation in a broad range of PCOS women (*i.e.* normal-weight and overweight patients). Moreover, our data show the effectiveness of metformin treatment not only for the ovulation induction but also in achieving a pregnancy. In particular, the cumulative ovulation rate over 6 months was not different between the metformin and CC groups, whereas the pregnancy rate was significantly higher with the use of metformin. In consideration of a NNT of 3, these data results are clinically remarkable.

A different trend was observed during the 6 months of treatment in the two therapeutical approaches. Specifically, whereas the efficacy of metformin increased throughout the study, a reduction in CC effectiveness was detected. The positive trend in ovulation and pregnancy rates observed in the present sample of anovulatory PCOS patients under metformin treatment was very similar to that observed in an our previous study in CC-resistant subjects (16), showing that metformin acts on reproductive functions of PCOS subjects independently from CC resistance.

The effect of metformin administration in pregnancy has been analyzed by several metaanalyses showing that metformin has no benefit *vs.* placebo, whereas metformin plus CC is about 3.5-fold more effective than CC alone (14, 15). Furthermore, a direct and appropriate comparison between metformin and CC has never been performed in any study.

This study is the first clinical trial having a head-to-head comparison between metformin and CC as the first-line treatment to ovulation induction in anovulatory PCOS patients. Although Legro and Myers (27) suggested the use of a primary outcome in clinical trials, the present study was powered on a surrogate clinical end point (*i.e.* cumulative pregnancy rate). Furthermore, this last end point has a strong correlation with the ideal primary outcome (*i.e.* healthy live births).

After 6 months of treatment, the abortion rate was significantly lower in PCOS women treated with metformin in

comparison with those treated with CC. The abortion rate observed in the metformin group was very low and comparable with those obtained in our previous trial (16). Because metformin was administered until the diagnosis of pregnancy (28), we can hypothesize that the known beneficial effects of metformin on pregnancy was exerted in our sample population by an action on oocytes and/or embryos and/or endometrium (29, 30). On the contrary, a high rate of abortion was detected in PCOS patients treated with CC. In this regard it has been already demonstrated that PCOS women have a high risk of abortion (31), and CC probably increases this risk (5, 11).

Although no randomized, controlled trial has been conducted to study the efficacy of metformin in obese *vs.* nonobese women with PCOS, there are contrasting data regarding the effectiveness of metformin in PCOS patients with different BMI (32–34). Morin-Papunen *et al.* (34) showed that metformin is effective in obese PCOS patients, whereas it was previously demonstrated that nonobese women with PCOS have a higher benefit from metformin administration than obese PCOS patients (32, 33). In addition, a well-recognized relationship was observed between obesity and abortion and/or complicated pregnancy (35, 36). For these reasons, we selected only nonobese PCOS women as a study population.

Another important confounding factor in several studies is the weight loss as an independent factor for the improvement of the menstrual cyclicity, ovulation, and fertility (37–39). Certainly lifestyle changes are a first-line intervention in women with PCOS who are obese. In this view, PCOS subjects who intended to start a diet or increase their physical activity were encouraged but excluded from the present study protocol to avoid the interference of this pivotal factor. For the same reasons, women who also had diet- or physical activity-related weight changes throughout the study were excluded from the final analysis.

Both metformin and CC were similarly well tolerated, and only in a very low percentage of cases was the treatment suspended for the appearance of drug-related AEs. Gastrointestinal side effects were observed during metformin administration, whereas the CC-related AEs consisted of hypoestrogenic symptoms.

In conclusion, our results demonstrate that both CC and metformin administration are two similarly and highly effective drugs for inducing regular ovulatory cycles in nonobese anovulatory women with PCOS. The higher cumulative pregnancy rate observed with metformin treatment demonstrates that metformin is more effective than CC in treating the anovulatory infertility in nonobese PCOS women. Data on a larger sample are also needed to demonstrate the effect on live-birth rate.

Acknowledgments

The authors thank all of the gynecological units of the Calabria and Campania regions that have given their help in the subjects' enrollment.

Received January 19, 2005. Accepted April 6, 2005.

Address all correspondence and requests for reprints to: Stefano Palomba, M.D., Department of Gynecology and Obstetrics, University "Magna Graecia" of Catanzar, Via Nicolardi 188, 80131 Naples, Italy. E-mail: stefanopalomba@tin.it.

References

1. **Frank S** 1995 Polycystic ovary syndrome. N Engl J Med 333:853–861
2. **Zawadzki JK, Dunaif A** 1992 Diagnostic criteria for polycystic ovary syndrome: toward a rational approach. In: Dunaif A, Givens JR, Haseltine FP, Merriam GR, eds. Polycystic ovary syndrome. Boston: Blackwell; 337–384
3. **Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group** 2004 Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 81:19–25
4. **Hamilton-Fairley D, Taylor A** 2003 Anovulation. BMJ 327:546–549
5. **Palomba S, Orio Jr F, Russo T, Falbo A, Cascella T, Colao A, Lombardi G, Zullo F** 2004 Is ovulation induction still a therapeutic problem in patients with polycystic ovary syndrome? J Endocrinol Invest 27:796–805
6. **Holtkamp DE, Greslin JG, Root CA, Lerner LJ** 1960 Gonadotropin inhibiting and anti-fecundity effects of chloramiphene. Proc Soc Exp Biol Med 105:197–201
7. **Greenblatt RB, Barfield WE, Jugck EC, Ray AW** 1961 Induction of ovulation with MRL-41: preliminary report. JAMA 178:225
8. **Greenblatt RB** 1961 Chemical induction of ovulation. Fertil Steril 12:402–404
9. **Adashi EY** 1984 Clomiphene citrate: mechanism(s) and site(s) of action. A hypothesis revisited. Fertil Steril 42:331–334
10. **Hughes E, Collins J, Vandekerckhove P, Lilford R** 2000 Clomiphene citrate for ovulation induction in women with oligo-amenorrhoea. Cochrane Database Syst Rev CD000056
11. **Kousta E, White DM, Franks S** 1997 Modern use of clomiphene citrate in induction of ovulation. Hum Reprod Update 3:359–365
12. **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
13. **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
14. **Lord JM, Flight IH, Norman RJ** 2003 Metformin in polycystic ovary syndrome: systematic review and meta-analysis. BMJ 327:951–953
15. **Kashyap S, Wells GA, Rosenwaks Z** 2004 Insulin-sensitizing agents as primary therapy for patients with polycystic ovarian syndrome. Hum Reprod 19:2474–2483
16. **Palomba S, Orio Jr F, Nardo LG, Falbo A, Russo T, Corea D, Doldo P, Lombardi G, Tolino A, Colao A, Zullo F** 2004 Metformin administration versus laparoscopic ovarian diathermy in clomiphene citrate-resistant women with polycystic ovary syndrome: a prospective parallel randomized double-blind placebo-controlled trial. J Clin Endocrinol Metab 89:4801–4809
17. **Norman RJ** 2004 Metformin—comparison with other therapies in ovulation induction in polycystic ovary syndrome. J Clin Endocrinol Metab 89:4797–4800 (Editorial)
18. **Heiat A** 2003 Impact of age on definition of standards for ideal weight. Prev Cardiol 6:104–107
19. **Orio Jr F, Palomba S, Di Biase S, Colao A, Tauchmanovà L, Savastano S, Labella D, Russo T, Zullo F, Lombardi G** 2003 Homocysteine levels and C677T polymorphism of methylenetetrahydrofolate reductase in women with polycystic ovary syndrome. J Clin Endocrinol Metab 88:673–679
20. **Modan M, Harris MI, Halkin H** 1989 Evaluation of WHO and NDDG criteria for impaired glucose tolerance. Results from two national samples. Diabetes 38:1630–1635
21. **Tai MM** 1994 A mathematical model for the determination of total area under glucose tolerance and other metabolic curves. Diabetes Care 17:152–154
22. **Hatch R, Rosenfield RL, Kim MH, Tredway D** 1981 Hirsutism implications, etiology, and management. Am J Obstet Gynecol 140:815–830
23. **Palomba S, Orio Jr F, Colao A, Di Carlo C, Sena T, Lombardi G, Zullo F, Mastrantonio P** 2002 Effect of estrogen replacement plus low-dose alendronate treatment on bone density in surgically postmenopausal women with osteoporosis. J Clin Endocrinol Metab 87:1502–1508
24. **ESHRE Capri Workshop Group** 2003 Mono-ovulatory cycles: a key goal in profertility programmes. Hum Reprod Update 9:263–274
25. **Nugent D, Vandekerckhove P, Hughes E, Arnot M, Lilford R**2000 Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. Cochrane Database Syst Rev CD000410
26. **Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ** 1994 Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 43:647–654
27. **Legro RS, Myers E** 2004 Surrogate end-points or primary outcomes in clinical trials in women with polycystic ovary syndrome? Hum Reprod 19:1697–1704
28. **Norman RJ, Wang JX, Hague W** 2004 Should we continue or stop insulin sensitizing drugs during pregnancy? Curr Opin Obstet Gynecol 16:245–250
29. **Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA, Nestler JE** 2002 Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. J Clin Endocrinol Metab 87:524–529
30. **Mansfield R, Galea R, Brincat M, Hole D, Mason H** 2003 Metformin has direct effects on human ovarian steroidogenesis. Fertil Steril 79:956–962
31. **Sagle M, Bishop K, Ridley N, Alexander FM, Michel M, Bonney RC, Beard**

RW, Franks S 1988 Recurrent early miscarriage and polycystic ovaries. BMJ 297:1027–1028
32. **Fleming R, Hopkinson ZE, Wallace AM, Greer IA, Sattar N** 2002 Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. J Clin Endocrinol Metab 87:569–574
33. **Maciel GA, Soares Junior JM, Alves da Motta EL, Abi Haidar M, de Lima GR, Baracat EC** 2004 Nonobese women with polycystic ovary syndrome respond better than obese women to treatment with metformin. Fertil Steril 81:355–360
34. **Morin-Papunen LC, Koivunen RM, Ruokonen A, Martikainen HK** 1998 Metformin therapy improves the menstrual pattern with minimal endocrine and metabolic effects in women with polycystic ovary syndrome. Fertil Steril 69:691–696
35. **Bellver J, Pellicer A** 2004 Impact of obesity on spontaneous abortion. Am J Obstet Gynecol 190:293–294
36. **Linne Y** 2004 Effects of obesity on women's reproduction and complications during pregnancy. Obes Rev 5:137–143
37. **Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X, Norman RJ** 1995 Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Hum Reprod 10:2705–2712
38. **Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ** 1998 Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. Hum Reprod 13:1502–1505
39. **Crosignani PG, Colombo M, Vegetti W, Somigliana E, Gessati A, Ragni G** 2003 Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. Hum Reprod 18:1928–1932

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