Metformin Administration Versus Laparoscopic Ovarian Diathermy in Clomiphene Citrate-Resistant Women with Polycystic Ovary Syndrome: A Prospective Parallel Randomized Double-Blind Placebo-Controlled Trial

STEFANO PALOMBA, FRANCESCO ORIO, Jr., LUCIANO GIOVANNI NARDO, ANGELA FALBO, TIZIANA RUSSO, DOMENICO COREA, PATRIZIA DOLDO, GAETANO LOMBARDI, ACHILLE TOLINO, ANNAMARIA COLAO, AND FULVIO ZULLO

Departments of Obstetrics and Gynecology (S.P., A.F., T.R., D.C., F.Z.) and Experimental Medicine (P.D.), University “Magna Graecia” of Catanzaro, 88100 Catanzaro, Italy; Departments of Molecular and Clinical Endocrinology and Oncology (F.O., G.L., A.C.), and Obstetrics and Gynecology (A.T.), University “Federico II” of Naples, 80131 Naples, Italy; and Imperial College (L.G.N.), St. Mary’s Hospital, London W2 1NY, United Kingdom

At present, it is unclear what the role is of laparoscopic ovarian diathermy (LOD) and of metformin administration as second-line treatments for ovulation induction in women with polycystic ovary syndrome (PCOS) after failure of clomiphene citrate (CC) treatment. The aim of the present study was to compare in a randomized double-blind placebo-controlled fashion the effectiveness of LOD with metformin administration in the treatment of CC-resistant women with PCOS. A total of 120 overweight primary infertile anovulatory CC-resistant women with PCOS were enrolled and randomized into two groups of treatment. Group A underwent diagnostic laparoscopy, whereas group B underwent LOD. At hospital discharge, the patients were treated for 6 months with metformin cloridrate (group A; 850 mg twice daily) or with multivitamins (group B). The ovulation, pregnancy, abortion, and live-birth rates were evaluated. At the end of the study, the total ovulation rate was not statistically different between both treatment groups (54.8 vs. 55.1% in groups A and B, respectively), whereas the pregnancy (18.6 vs. 13.4%), the abortion (15.4 vs. 29.0%), and the live-birth (82.1 vs. 64.5%) rates were significantly (P < 0.05) different between the two groups. Our data show that metformin administration is more effective than LOD in overall reproductive outcomes in overweight infertile CC-resistant women with PCOS. (J Clin Endocrinol Metab 89: 4801–4809, 2004)
pregnancy in CC-resistant women with PCOS (19). The aim of the present study was to compare in a randomized, double-blind, placebo-controlled fashion the effectiveness of LOD compared with metformin administration in the treatment of CC-resistant women with PCOS.

Subjects and Methods

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 each patient, and a written consent was obtained from each subject before beginning the study.

Subjects

Between October 2001 and December 2002, a total of 120 overweight primary infertile anovulatory CC-resistant women with PCOS were enrolled. The diagnosis of PCOS was initially made according to the National Institutes of Health criteria (5). CC resistance was defined as failure to ovulate during a total of at least three consecutive cycles using doses of CC of 150 mg for 5 d from d 3–7 of withdrawal bleeding induced with medroxyprogesterone acetate. A body mass index (BMI) between 25 and 30 was considered as overweight (20).

Exclusion criteria for all subjects included age of less than 22 yr or more than 34 yr, hypothyroidism, hyperprolactinemia, Cushing’s syndrome, nonclassical congenital adrenal hyperplasia, and current or previous (within the last 6 months) use of oral contraceptives, glucocorticoids, antiandrogens, ovulation induction agents, antiabetic or antiobesity drugs, or other hormonal drugs. The presence of hyperprolactinemia was excluded considering the average value of serum prolactin i.e. 22 ng/ml (SI, < 15 μg/liter). In women with serum PRL levels greater than 25 ng/ml (SI, > 15 μg/liter), hyperprolactinemia was included considering the average value of serum PRL assayed at 0800 h for three times every 15 min.

Nonclassical congenital adrenal hyperplasia was excluded with a single measure of serum 17-hydroxyprogesterone (17-OHP) levels [normal value < 1.98 μg/liter (SI, 6.0 nmol/liter)].

No subject was affected by any neoplastic, metabolic, hepatic, or cardiovascular disorder or other concurrent medical illness (i.e., diabetes, renal disease, or malabsorptive disorders). Specifically, PCOS women with glucose intolerance, as assessed by World Health Organization criteria (21), were excluded from the study. We excluded also women who were intending to start a diet or a specific program of physical activity. Other exclusion criteria were organic pelvic diseases, previous pelvic surgery, suspected peri toneal factor infertility, and tubal or male factor infertility. Tubal infertility and male factor infertility were excluded with a hysterosalpingogram and with semen analysis, respectively.

All subjects were nonsmokers and had normal physical activity, and none drank alcoholic beverages.

Protocol and treatment

At study entry, all subjects had venous blood drawn to evaluate the complete hormonal assays, serum glucose and insulin levels. At baseline, in both groups we calculated the Ferriman-Gallwey score (22) and evaluated patients’ daily physical activity, job, and daily activities using a semiquantitative questionnaire (23).

During the same visit, all subjects underwent transvaginal ultrasonography (TV-USG) and 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 (kg/m²). 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 same experienced operator performed all measurements.

The subjects were randomly allocated into two treatment groups of 60 women each (groups A and B). The randomization was carried out using 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.

All subjects underwent laparoscopy. Specifically, diagnostic laparoscopies were performed in group A. For the duration of the study, each patient was blinded with regard to the surgical treatment performed.

At hospital discharge, group A was treated with metformin cloridrate (Metforal, Laboratori Guidotti, Pisa, Italy) at a dosage of 150 mg daily for five times from d 3–7 of postoperative (P)-induced uterine bleeding. Patients who conceived suspended the treatment (metformin or placebo tablets for groups A and B, respectively) (24–26).

At the end of the study, a 6-month extension of the follow-up period was performed to obtain the live-birth rate for each treatment group.

Each woman was asked to keep a time table every 2 d for longer times from the sonographic detection of a follicle with a mean diameter of at least 18 mm (detailed below).

Throughout the study, no changes in diet and in physical activity were implemented. On the contrary, the subjects were instructed to follow their usual diet and physical activity.

Standard clinical evaluations and laboratory analyses, 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.

The subjects were instructed to report in a daily diary the onset of any adverse experiences (AEs), specifying the severity, duration, and a possible cause-effect relationship with drug administration. To evaluate compliance with the treatment and with the protocol, the number of tablets forgotten, the changes in diet, physical activity, and weight, as well as the timing of intercourse were also recorded in the same diary.

Surgical procedures

The same experienced operator performed the laparoscopic procedures. After induction of general anesthesia, the patient was placed in the low lithotomic position to perform pelvic laparoscopy and vaginal manipulations. Immediately before surgery, an antibiotic therapy was given iv. A Foley catheter was inserted. After executing a pneumoperitoneum using a Verres needle, a 10-mm videolaparoscope was inserted umbilically, followed by the lateral insertion of two 5-mm ancillary trocars in the left and right iliac fossa. A careful inspection of the pelvic cavity was performed in each patient. Only in group B the LOD followed the diagnostic procedure. The LOD was performed as previously described by Tulandi (27). The ovary was immobilized with a laparoscopic forceps, and three to six punctures were performed with an insulated needle cautery of 36 mm (Karl Storz GmbH and Co. KG, Tuttingen, Germany). The needle was inserted for its whole length as perpendicularly as possible to the ovarian surface after setting the electrosurgical device (Erbotom ACC 450, Erbe GmbH, Tubingen, Germany) at a cutting current of 100 W power. The monopolar coagulating current was then set at 40 W power, and the needle was activated for 2–3 sec at each point. The number of punctures made in each ovary depended on its size. At completion of the procedure, the ovarian surface was washed with a crystallloid solution. The injured areas were completely covered with hyaluronic acid gel (Hyalobarrier gel, Baxter, Pisa, Italy) (28).

Duration of surgical procedure, blood loss, and hospital stay were recorded. All intra- and postoperative complications were carefully recorded for each group. Based on clinical conditions, patients were discharged either on the same day of the surgical procedure or 1 d postoperatively.
Biochemical assays

All blood samples were obtained in the morning between 0800 and 0900 h after an overnight fast (at least 12 h) and a 30-min resting in the supine position during the early proliferative phase (d 2–3) of the spontaneous or P-induced withdrawal uterine bleeding. Blood samples (5 ml) were collected into tubes containing EDTA and were immediately centrifuged at 4 C for 20 min at 1600 × g, and plasma samples were stored at −20 C.

Plasma LH, FSH, PRL, estradiol, P, 17-OHP, testosterone (T), androstenedione, and dehydroepiandrosterone sulfate were measured by specific RIA as previously reported (29). SHBG levels were measured also using an immunoradiometric assay (29). 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 (29).

In each woman, the free androgen index (FAI) was calculated using the following formula: T (nmol/liter)/SHBG × 100 (30). Glucose and insulin values were detected also after an oral glucose tolerance test (OGTT). Glucose and insulin concentrations were measured also 30 min after insertion of the iv catheter to detect the fasting levels (time 0) before OGTT. Subsequently, each subject received orally a 75-g glucose load. Additional blood samples (10 ml each) were obtained at 30-min intervals for the next 3 h during the infusion period (times 30, 60, 90, and 120 min), and glucose and insulin concentrations were determined. Glucose tolerance was assessed by World Health Organization criteria (21). In both groups, the glucose and insulin response to OGTT was analyzed by calculating the area under the curve (AUC). The AUC for glucose (AUCglucose) and insulin (AUCinsulin) were determined according to the mathematical method described by Tai (31) for the metabolic variables. The AUCglucose/AUCinsulin ratio was also calculated in each subject (29).

Clinical outcomes

The subjects were instructed to report in a daily diary the characteristics of their menstrual cycles. Specifically, the length and the frequency of the menstrual bleedings were evaluated. The frequency of menstrual cycles was evaluated as the percentage of observed menses relative to the number of expected menses.

The quantity of the cyclical uterine bleedings was also evaluated subjectively by each woman using a rank analog scale ranging from 1–10. 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.

Reproductive outcomes

During the 6 months of treatment, the ovulation, pregnancy, abortion, and live-birth rates were evaluated in each woman.

The ovulatory cycles were evaluated using TV-USG measurements. The scans were performed by the same experienced operator every 3 d, starting on d 7 after intervention (during the first month from surgery), and subsequently on d 2 after the onset of menses using an ultrasonic scanner (Aplio, Toshiba Medical Systems, Rome, Italy) equipped with a 7.5-MHz vaginal probe. When the follicular dimensions achieved at least 16 mm, the TV-USG was performed daily. Follicular development was studied by measuring the two main diameters of the follicle. The day of ovulation was retrospectively defined with the observation of decreased follicular dimensions and of liquid in the cul-de-sac and confirmed by a plasma F assay >10 ng/ml (>31.8 nmol/liter, SI units).

Ovulation rate was calculated as the percentage of ovulatory cycles relative to total cycles. Pregnancy rate was defined as the percentage of pregnancies relative to total cycles. A rising β-human chorionic gonadotropin level and the sonographic evidence of intrauterine gestational sac were considered criteria to define a pregnancy. Abortion rate was defined as the percentage of miscarriages during the first 12 wk of gestation relative to total pregnancies. Live-birth rate was defined as the percentage of women with baby alive relative to women who achieved a pregnancy.

Cost of the treatments

A comparison in terms of costs was performed between LOD and metformin treatment.

To assess the cost of LOD, we considered the day-surgery fee, the surgeon’s fee, the anesthetist’s fee, and assistant’s fee as absolute costs in euros. All equipment and the disposables used to perform diagnostic or operative laparoscopies were resterilized and provided by the Laparoscopic Center of the University of Catanzaro. Thus, no additional cost was calculated for the surgical equipment.

The cost of medical therapy was determined considering the average cost of six cycles of metformin cloridrate administration at doses of 1700 mg daily.

Statistical analysis

The primary endpoint of our study was the ovulation rate. Based on the assumption that the expectant ovulation rate is 70% in the control group (LOD only) (12) and that a difference in ovulation rate is clinically relevant only for differences higher than 20%, we needed to enroll 60 patients for each group to demonstrate a difference of 20% between control and experimental groups (metformin group) and to define statistical significance between the groups with α = 0.05 and β = 0.20.

The demographic and biochemical data were analyzed by the Student’s t test for unpaired data. The Mann-Whitney U test for independent groups of data was used to compare hospital stay, physical activity, duration of operation, and intraoperative blood loss. The Fisher exact test was used to compare the incidences of complications and of AEs between treatment groups. The differences in length of the menses at different times of treatment were calculated using ANOVA for repeated measures with Bonferroni’s test for multiple comparisons. Wilcoxon’s rank-sum test was used to compare the quantity of the menses between and within groups. The frequency (percentage) of menstrual cycles was also analyzed with the use of the χ2 test. Ovulation, pregnancy, abortion, and live-birth rates were also evaluated using the χ2 test. The costs of the two treatments were also compared with the use of the Student’s t test for unpaired data.

Data were analyzed using the intention-to-treat method and expressed as mean ± sd. A P value < 0.05 was considered statistically significant. The Statistics Package for Social Science (SPSS 11.0, SPSS Inc., Chicago, IL) was used for statistical analyses.

Results

An overview of the trial is shown in Fig. 1.

Demographic and hormonal data

Patients’ characteristics are presented in Table 1. After randomization, the two groups were similar for age and BMI. No difference in WHR, duration of infertility, Ferriman-Gallwey score, physical activity score, or any biochemical assay was observed between the two groups (Table 1). Also, no difference between groups was detected in FAI and in glucose and insulin levels (Table 1).

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

Dropouts

The numbers of withdrawals were similar in the two groups (six and five women in groups A and B, respectively). Specifically, six patients (four and two in groups A and B, respectively) were excluded after laparoscopy for the presence of minimal endometriosis. One woman from each group was excluded by final analysis for lack of compliance with the treatment (they did not take tablets during the first 3 wk for drug-related AEs). Finally, one
A woman from group A and two women from group B were excluded because a reduction in body weight (>5% from basal value) was observed after the first 3 months of the study.

Results included in this study were obtained from a total of 109 patients (mean age, 27.2 ± 2.4 yr; range, 24–30 yr), 54 and 55 women in groups A and B, respectively.

**TABLE 1.** Clinical, hormonal, and metabolic data of PCOS women treated with diagnostic laparoscopy plus metformin (group A) or LOD plus placebo (group B) at study entry

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 60)</th>
<th>Group B (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>26.8 ± 2.2</td>
<td>27.5 ± 2.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.1 ± 1.7</td>
<td>27.6 ± 1.6</td>
</tr>
<tr>
<td>WHR</td>
<td>0.87 ± 0.4</td>
<td>0.86 ± 0.3</td>
</tr>
<tr>
<td>Duration of infertility (months)</td>
<td>25.8 ± 7.4</td>
<td>23.4 ± 5.8</td>
</tr>
<tr>
<td>Ferriman-Gallwey score</td>
<td>13.5 ± 1.8</td>
<td>12.6 ± 1.6</td>
</tr>
<tr>
<td>Physical activity score</td>
<td>1.8 ± 0.4</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>10.5 ± 1.5</td>
<td>9.8 ± 1.8</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>24.6 ± 1.5</td>
<td>18.6 ± 3.7</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>12.4 ± 1.1</td>
<td>13.1 ± 1.2</td>
</tr>
<tr>
<td>E₂ (pg/ml)</td>
<td>38.5 ± 5.7</td>
<td>36.1 ± 5.2</td>
</tr>
<tr>
<td>P (ng/ml)</td>
<td>0.4 ± 0.2</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>17-OHP (μg/liter)</td>
<td>14.9 ± 0.5</td>
<td>15.0 ± 0.6</td>
</tr>
<tr>
<td>T (ng/ml)</td>
<td>0.8 ± 0.1</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>A (ng/ml)</td>
<td>1.6 ± 0.2</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>DHEAS (μg/liter)</td>
<td>2259 ± 124</td>
<td>2311 ± 112</td>
</tr>
<tr>
<td>SHBG (nmol/liter)</td>
<td>28.4 ± 6.1</td>
<td>27.0 ± 5.3</td>
</tr>
<tr>
<td>FAI (%)</td>
<td>14.8 ± 6.7</td>
<td>15.5 ± 7.5</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>98.3 ± 8.9</td>
<td>95.9 ± 7.8</td>
</tr>
<tr>
<td>Fasting insulin (μU/ml)</td>
<td>18.8 ± 5.5</td>
<td>20.8 ± 5.7</td>
</tr>
<tr>
<td>OGTT AUCglucose</td>
<td>1109 ± 542</td>
<td>1163 ± 561</td>
</tr>
<tr>
<td>AUCinsulin</td>
<td>5399 ± 1374</td>
<td>5976 ± 1321</td>
</tr>
<tr>
<td>AUCglucose/AUCinsulin ratio</td>
<td>0.21 ± 0.16</td>
<td>0.19 ± 0.27</td>
</tr>
</tbody>
</table>

Physical activity was scored as follows: 1 = low; 2 = moderate; 3 = high. Data are expressed as mean ± sd. The biochemical assays are reported in metric units. Conversion factors for SI are as follows: androstenedione (A) = 3.492 (nmol/liter); dehydroepiandrosterone sulfate (DHEAS) = 0.02714 (mmol/liter); estradiol (E₂) = 3.671 (pmol/liter); FSH = 1 (IU/liter); glucose = 0.05551 (mmol/liter); insulin = 7.175 (pmol/liter); LH = 1 (IU/liter); 17-OHP = 3.026 (nmol/liter); P = 3.180 (nmol/liter); PRL = 1 (mg/liter); T = 3.467 (nmol/liter).

Surgical results

Before surgery, the red blood cell count, hematocrit, serum hemoglobin, and iron levels were not statistically different between the two groups. The same parameters were also similar in both groups after surgical intervention (data not shown). In particular, the difference between serum hemoglobin levels measured before and after surgery was similar in both groups (0.49 ± 0.17 vs. 0.35 ± 0.16 for groups A and B, respectively).

Laparoscopies were completed successfully in all women, and no case was converted to laparotomy. No difference in surgical complications was detected between the two groups. No significant differences were observed between groups in operative time (min ± sd, 16.6 ± 3.2 vs. 19.2 ± 4.3 for groups A and B, respectively) or in postoperative hospital stay (days ± sd, 0.52 ± 0.24 vs. 0.51 ± 0.23 for groups A and B, respectively). No intraoperative or postoperative complications were detected in either group.

In two cases for each treatment group, we observed a minimal endometriosis (32) that was treated with a conservative approach consisting of electrocauterity ablation or excision of visible pelvic endometriotic lesions. A histological analysis of the lesions was also performed to confirm the diagnosis.

Clinical outcomes

No difference in the length (Fig. 2) or in the quantity (data not shown) of menstrual bleedings was observed throughout the study.

The frequency of the menstrual cycles was similar between the two treatment groups (Fig. 3).
Reproductive outcomes

In Table 2 are detailed the ovulation and pregnancy rates for each month of observation in both treatment groups. Table 3 summarizes the reproductive outcomes observed during the study in both treatment groups.

The subjects of groups A and B were studied for a total of 210 and 231 cycles, respectively. At the end of the study, the total ovulation rate was not statistically different between both treatment groups (54.8 % vs. 55.1 % in groups A and B, respectively). The pregnancy rate was significantly \( (P < 0.05) \) higher in group A in comparison with group B (18.6 % vs. 13.4 % in groups A and B, respectively). The abortion rate was significantly \( (P < 0.05) \) lower in group A in comparison with group B (15.4 % vs. 29.0 % for groups A and B, respectively). The live-birth rate was significantly \( (P < 0.05) \) higher in group A than in group B (82.1 % vs. 64.5 % in groups A and B, respectively). None of the women had multiple pregnancies.

After six cycles of treatment, the cumulative pregnancy rate was 72.2 % (39 of 54) and 56.4 % (31 of 55) for groups A and B, respectively.

At the end of the six-cycle treatment, 3 of 15 and 4 of 24 PCOS women in groups A and B, respectively, had regular ovulatory menstrual cycles. The other women were still oligo- or amenorrheic.

Side effects

Throughout 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.

The incidence of drug-related AEs due to metformin was, furthermore, significantly \( (P < 0.05) \) higher in comparison with placebo. Specifically, during the first months of treatment, 12 of 54 women (22.2 %) treated with metformin reported diarrhea, flatulence, and nausea, whereas three of 55 women (5.5 %) treated with placebo reported gastralgia and constipation. No serious AEs were reported during the study.

Economic data

In Table 4 are shown the costs of an episode of LOD performed in a day-surgery center with the costs of 6 months of treatment with metformin. The LOD was significantly \( (P < 0.05) \) more expensive in comparison with 6 months of metformin administration (1050 euros vs. 50 euros).

Discussion

PCOS is associated with approximately 75 % of women who suffer from infertility caused by anovulation (2–4). It is generally accepted that the first line of treatment to induce ovulation in PCOS women is CC administration (7, 8). Despite treatment with CC, a variable percentage of PCOS women remains anovulatory or does not achieve a pregnancy. In fact, the ovulation rate after CC treatment is approximately 70–80 % with a pregnancy rate of approximately 40 % (7, 8).

### TABLE 2. Ovulation and pregnancy rates in PCOS women treated with diagnostic laparoscopy plus metformin (group A) or LOD plus placebo (group B) for each month of follow-up

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Ovulation rate [no. ovulatory cycles/no. cycles (%)]</th>
<th>Pregnancy rate [no. pregnancies/no. cycles (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>1</td>
<td>21/54 (38.9)</td>
<td>27/55 (49.1)</td>
</tr>
<tr>
<td>2</td>
<td>24/46 (52.2)</td>
<td>26/47 (55.3)</td>
</tr>
<tr>
<td>3</td>
<td>23/37 (62.2)</td>
<td>20/38 (52.6)</td>
</tr>
<tr>
<td>4</td>
<td>19/30 (63.3)</td>
<td>19/34 (55.8)</td>
</tr>
<tr>
<td>5</td>
<td>16/24 (66.6)</td>
<td>17/30 (56.7)</td>
</tr>
<tr>
<td>6</td>
<td>12/19 (63.2)</td>
<td>14/27 (51.8)</td>
</tr>
</tbody>
</table>

\( a P < 0.05 \) vs. group A.

### TABLE 3. Reproductive outcomes in PCOS women treated with diagnostic laparoscopy plus metformin (group A) or LOD plus placebo (group B)

<table>
<thead>
<tr>
<th>Reproductive outcomes</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation rate [no. ovulating cycles/no. cycles (%)]</td>
<td>115/210 (54.8)</td>
<td>123/231 (53.3)</td>
</tr>
<tr>
<td>Pregnancy rate [no. pregnancies/no. cycles (%)]</td>
<td>39/210 (18.6)</td>
<td>31/231 (13.4)</td>
</tr>
<tr>
<td>Abortion rate [no. abortions/no. pregnancies (%)]</td>
<td>6/39 (15.4)</td>
<td>9/31 (29.0)</td>
</tr>
<tr>
<td>Live-birth rate [no. babies/no. pregnancies (%)]</td>
<td>32/39 (82.1)</td>
<td>20/31 (64.5)</td>
</tr>
</tbody>
</table>

\( a P < 0.05 \) vs. group A.
Only a few years ago, the second-line treatments in CC-
resistant PCOS women consisted of LOD or gonadotropins
use. The two approaches are similar in terms of ovulation and
pregnancy rates (33–37). Furthermore, during gonadotropins
administration, a particular experience of the operator is
needed as well as careful sonographic and biochemical mon-
toring to avoid or to reduce the risk of ovarian hyperstimu-
lation and multiple pregnancies, particularly in PCOS sub-
jects. In addition, the treatment with gonadotropins requires
a relevant investment of time and of money (33). On the
contrary, with the advent of laparoscopic techniques and
with their wide use, LOD has been proposed as a once-only
procedure to induce ovulation in CC-resistant PCOS women
(12).
LOD is a day-surgery procedure characterized not only by
an effectiveness in ovulation induction comparable to go-
adotropin use (10, 37) but also by few side effects and no
need for ongoing monitoring (7–10). In addition, LOD has
beneficial effects also at the metabolic level with an effect-
viveness that seems to be maintained after a long-term
follow-up (38–44). Despite these favorable aspects, LOD is
an invasive procedure that can be associated with pelvic
adhesions formation (11–15).
At present, several studies (7, 16–18) have highlighted the
possibility to use drugs with insulin-sensitizing action in
PCOS patients to induce simple ovulation in CC-resistant or
nonresistant patients. In particular, metformin, an oral bi-
guanide administered in type-2 diabetes mellitus, has been
shown to be effective in PCOS patients in terms of menstrual
cyclicity and/or ovulation both in observational (45–51) and
randomized controlled trials (52–54). Metformin increases
the ovulation rate in patients later treated with CC (16) and
improves the response to CC in CC-resistant PCOS patients
(55, 56). Few and insufficient data are available in the liter-
ature regarding the administration of metformin in PCOS
patients treated with gonadotropins (56–59).
It is not completely certain whether metformin adminis-
tration is effective in lean PCOS patients (60, 61) because
these subjects are less insulin resistant than obese PCOS
patients (62). On the contrary, it is possible that nonobese
women with PCOS receive a similar benefit from metformin
administration such as obese and/or overweight PCOS pa-
tients (63). In addition, metformin does not seem to improve
or seem to have minor effects on the reproductive and
endocrine outcomes in extremely obese patients with a BMI
higher than 35 kg/m² (64). With this view, in the present
study we enrolled only overweight women to eliminate a
possible confounding factor.
Another important confounding factor in several studies is
weight loss as an independent factor improving menstrual
cyclicity, ovulation, and fertility (65–67). Certainly, lifestyle
changes are a first-line intervention in women with PCOS
who are obese (or overweight). In this view, PCOS subjects
who intended to start a diet or to increase their physical
activity were encouraged but excluded from the present
study protocol to avoid the interference of this pivotal factor.
In addition, women who had diet- or physical activity-
related weight changes throughout the study were also ex-
cluded from final analysis.
At present, only one study (19) has compared the efficacy of
metformin with LOD alone in the treatment of CC-resis-
tant women with PCOS. Furthermore, in this last study (19),
if spontaneous ovulation or pregnancy was not achieved
within only 3 months of treatment, CC was added with
increments of 50 mg for both treatment groups. In addition,
no laparoscopy was performed in the metformin group and
no placebo tablets were administered in the LOD group. A
significant improvement in the regularity of menstrual cycles
and in the rates of ovulation and pregnancy was observed,
with no difference between metformin administration and
LOD. The authors (19) concluded that CC-resistant patients
with PCOS can be treated effectively either by LOD or met-
formin without differences between treatments in terms of
menstrual cyclicity and of ovulation and pregnancy rates.
Our results confirm (19) that either LOD or metformin
administration are similarly effective in inducing regular
ovulatory cycles in a high percentage of anovulatory PCOS
women. Moreover, our data show a significant difference
between groups in pregnancy rate. At present, controversial
and few data exist on the reduction of fertility caused by
postoperative pelvic adhesions followed by laparoscopy.
Certainly, laparoscopy reduces significantly the adhesions
rate in comparison with laparotomy, but it is still unknown
how much this rate should be reduced to have an effect on
reproductive outcomes and whether the filmy adhesions ob-
served also after diagnostic laparoscopy could play a role.
For these reasons, a diagnostic laparoscopy was performed
in women treated with metformin to remove another con-
founding factor.
Our study confirms (33) that the routinely diagnostic lapa-
roscopy should be avoided in infertile women without a
clinical and diagnostic suspicion of peritoneal disease. In
fact, in our selected series, in only 5% of cases (six of 120
women) was a mild endometriosis observed and treated.
As already reported by Fleming et al. (53), we observed
during the first months of metformin treatment a rapid effect
on the reproductive system. The ovulation and the preg-
nancy rates were constant throughout the 6 months of met-
formin administration. Based on these results, we feel that
metformin administration should be used for at least 6
months and that the addition of CC could also start after this
period in CC-resistant women.
It is well known that the abortion rate in PCOS women is
generally higher than in healthy women (68–70) and that a

### TABLE 4. Comparison between costs of LOD and 6 months of metformin administration

<table>
<thead>
<tr>
<th>LOD</th>
<th>Metformin cloridrate treatment (850 mg twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day-surgery fee = 400 €</td>
<td>One pack of metformin cloridrate (30 cps of 850 mg each) = 4.18 €</td>
</tr>
<tr>
<td>Surgeon’s fee = 350 €</td>
<td>1 month of treatment = 4.18 € × 2 = 8.36 €</td>
</tr>
<tr>
<td>Assistant’s fee = 100 €</td>
<td>6 months of treatment = 8.36 € × 6 = 50.16 €</td>
</tr>
<tr>
<td>Total = 1050 €</td>
<td>Total = 50.16 €</td>
</tr>
</tbody>
</table>


high percentage of women with recurrent abortions are affected by PCOS (71–75). In the present study, the abortion rate was significantly lower in PCOS women treated with metformin in comparison with the LOD group. In the LOD group, the abortion rate was similar to those reported in PCOS women, whereas in the metformin group it was similar to healthy women (26–28, 74, 75). These findings, obtained with metformin administration until the diagnosis of pregnancy was made, could be caused by a beneficial effect of metformin on oocytes, embryos, and/or endometrium (26–28, 76–80).

No serious AEs were reported during the study in either group, and the metformin was generally well tolerated. Furthermore, the incidence of gastrointestinal side effects was significantly higher in the metformin group, but these symptoms were self-limiting and presented during the first months of treatment. Only three women suspended the treatment for the appearance of drug-related AEs. In agreement with Nestler’s suggestion (81), we feel that in clinical practice metformin administration should start with lower doses and should be progressively increased only after the first weeks.

An important issue followed by our study is the cost-benefit evaluation of the two protocols of management in the presence of a CC-resistant PCOS woman. Our data show that the cost of 6 months of metformin administration is approximately 20-fold less expensive than LOD. Recently, Kovacs et al. (82) have shown that LOD should be considered a second-line treatment in CC-resistant PCOS patients because its costs are significantly lower in comparison with gonadotropins use. Furthermore, we feel that these two previous therapeutic approaches should be not compared because they are conceptually too different.

In conclusion, our data show that either LOD or metformin administration is effective to induce ovulation in CC-resistant women with PCOS. A significant advantage in metformin administration seems to be related to a major improvement of pregnancy, abortion, and live-birth rates. In addition, metformin is less expensive than LOD and it doesn’t carry the usual risks of laparoscopy and general anesthesia. Based on these considerations, we feel that, at present, in an infertile anovulatory PCOS woman, LOD should be performed only during laparoscopy performed for suspected peritoneal factor or for other gynecological diseases. On the contrary, metformin administration, also as a single agent, can be considered the second-step approach to induce ovulation in PCOS women with CC resistance.

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

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