Metformin effects on ovarian ultrasound appearance and steroidogenic function in normal-weight normoinsulinemic women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial

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Objective: To investigate metformin effects on the endocrine-metabolic parameters and ovarian morphology in normoinsulinemic women with polycystic ovary syndrome (PCOS).

Design: Randomized double-blind study.

Setting: Operative Division of Endocrinological Gynecology, Università Cattolica del Sacro Cuore.

Patient(s): Twenty-eight normal-weight normoinsulinemic PCOS women.

Intervention(s): Patients were randomized to receive metformin 500 mg twice a day (group A, 15 subjects) or placebo (group B, 13 subjects) for 6 months. Ultrasonographic pelvic exams, hormonal and lipid features, and oral glucose tolerance test were performed at baseline and after 3 and 6 months of treatment.

Main Outcome Measure(s): Hormonal and glycoinsulinemic assessment, ovarian ultrasound appearance.

Result(s): Glycoinsulinemic assessment remained unvaried in both groups. About 70% of patients in group A experienced a restoration of menstrual cyclicity. Metformin significantly decreased testosterone levels at 3 and 6 months and 17-hydroxyprogesterone levels at 6 months, and improved hirsutism score at 6 months. No clinical or hormonal modifications occurred in group B. Metformin, but not placebo, reduced ovarian volume and stromal/total area ratio at 3 and 6 months.

Conclusion(s): Metformin seems to improve the menstrual pattern and ultrasonographic ovarian features in normoinsulinemic PCOS women. These effects seem to be, at least in part, independent of the insulin-lowering properties of the drug. (Fertil Steril 2010;93:2303–10. ©2010 by American Society for Reproductive Medicine.)

Key Words: Metformin, PCOS, ovaries, normoinsulinemic, normal-weight

Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic disorder occurring in ~5%–10% of women in reproductive age. Hyperandrogenism, chronic anovulation, and infertility are the main features of this heterogeneous condition (1). Although the pathogenesis of the syndrome is still unclear, several authors have suggested that insulin resistance, hyperinsulinemia, and obesity, which affect most PCOS patients, may play a pivotal role (2). The increased insulin circulating concentrations, indeed, seem to contribute to the etiology of hyperandrogenism by acting at several levels of the hypothalamic-pituitary-ovarian axis as well as on the hepatic production of sex hormone–binding globulin (SHBG). Actually, at ovarian level, insulin promotes androgen secretion by playing a synergistic role with gonadotropins both directly and by stimulating insulin-like growth factor I (IGF-I) secretion (3); in the liver, it decreases serum SHBG synthesis (4).

It is well known that there is a close relationship between elevated androgen plasma levels and the ultrasound finding of stromal hypertrophy (5). In particular, in previous studies, we demonstrated that the polycystic ovary is characterized by a higher stromal area/total area (S/A) ratio compared with multifollicular and normal ovaries, thus suggesting that an augmented ovarian stroma could represent the morphologic expression of increased androgen synthesis (6–7).

The evidence that the main metabolic imbalance of PCOS is represented by insulin resistance has led to a growing interest in insulin-sensitizing drugs as the preferable therapeutic approach to the syndrome. Metformin is a drug belonging...
to the biguanide class and, previously used in obese patients
with type 2 diabetes mellitus, has been recently proposed as
a first-line treatment in obese or overweight PCOS women
with hyperinsulinemia. In randomized trials, the administra-
tion of metformin was followed by an improvement in insulin
sensitivity, body mass index (BMI), and menstrual pattern
and a decrease of androgen levels in most women under
treatment (8).

Based on the favorable profile of action in obese PCOS pa-
tients, the effects of metformin were also investigated in nor-
mal-weight patients affected by the syndrome: most studies
documented a significant decrease in fasting insulin and an-
drogen levels, as well as a restoration of menstrual cyclicity
(9–10).

Because in normoinsulinemic women the beneficial effect
on the hormonal pattern was observed even after minimal
metabolic changes (11), it could be hypothesized that metfor-
min may also modulate the ovarian androgen discharge
through an insulin-independent route of action on the gonad.

The possible clinical impact of such a mechanism on the
reproductive function and, especially, the consequences on
the therapeutic strategy were never previously evaluated in
literature.

In the present study, we sought to investigate the effect, if
any, of metformin administration in normal-weight PCOS
women on the clinical-endocrine parameters and on the ultra-
sound appearance of the ovary, and the possible correlation
between these two aspects.

MATERIALS AND METHODS

Patients

We enrolled 28 normal-weight women with PCOS (BMI 22.4
± 3.9 kg/m², age range 19–32 yrs) attending our divisional
outpatient services. All women had spontaneous onset of pu-
berty and normal sexual development, and all had oligome-
norhea with chronic anovulation variably associated with
mild to moderate hirsutism. All of the women were euthy-
rroid, and none had taken medications known to affect plasma
sex steroids for at least 3 months before the study. In accor-
dance with the Rotterdam Consensus criteria (12), PCOS
was diagnosed in the presence of at least two of the three fol-
lowing clinical findings: chronic anovulation, clinical and/or
biochemical evidence of hyperandrogenism, and ultrasono-
graphic appearance of polycystic ovaries. The menstrual pat-
terns were defined according to van Hooff et al. (13). A
normal LH/FSH ratio was not considered to be an exclusion
criterion (7). The presence of a late-onset adrenal enzyme de-
fect was excluded by an ACTH test (250 µg IV Synacthen;
Ciba-Geigy, Basel, Switzerland) according to published cri-
teria of New et al. (14). Significant liver (aspartate amino-
transferase, alanine aminotransferase, total bilirubin, or
alkaline phosphatase >2 times the upper limit of normal)
or renal (serum creatinine >1.8 ng/dL) impairment, neo-
plasm, cardiovascular disease, diabetes mellitus, and unstab-
le mental illness were considered to be exclusion criteria.

Informed consent was obtained from each patient, and the
study protocol was approved by our Institutional Review
Board.

Because of the impact of body fat distribution on androgen
levels and glucose metabolism (15–16), waist-to-hip ratios
(WHRs) were measured. Waist circumference was deter-
mined as the minimum value between the iliac crest and
the lateral costal margin, whereas hip circumference was de-
termined as the maximum value over the buttocks. Cut-off
point for high WHR for women was set at 0.80 (17).

The grade of hirsutism was established using the Ferriman-
Galwey (FG) score (18), in which hair growth in each of 11
androgen-sensitive zones is graded from 0 (none) to 4
(frankly virile). On the basis of this method, four hirsutism
levels were identified: score <8, no hirsutism; score of 8–
16, low hirsutism; score of 17–25, moderate hirsutism; and
score >25, severe hirsutism. We considered the change
from one level to a lower one to be clinically meaningful.

The ratio of testosterone (T)/SHBG × 100 was used to
calculate the free androgen index (FAI).

At baseline, during the early follicular phase of a spontane-
ous or induced (medroxyprogesterone acetate, 10 mg/d for 7
days) menstrual cycle (day 3–7), the patients were hospital-
ized and underwent gynecologic and medical examinations.
The same day, a transvaginal pelvic ultrasoundwas per-
formed on each patient using a 6.5 MHz endovaginal probe
(AUCS; Esaote, Genova, Italy). The ultrasound examinations
were performed by one of three well trained observers who
were not aware of the patient’s endocrine profiles.

Ovarian volume was calculated for each ovary using the
formula for a prolate ellipsoid: \( \pi/6 \times (D_1 \times D_2 \times D_3) \),
where \( D_1-D_3 \) represent the maximum diameter in the trans-
verse, anteroposterior, and longitudinal axes) (19).

The S/A ratio was calculated as ovarian stromal area, eval-
uated by outlining with the caliper the peripheral profile of
the stroma identified by a central area slightly hyperechoic,
with respect to the total area of the ovary evaluated by outlin-
ing with the caliper the external limits of the ovary in the
maximum plane section.

The mean ovarian volume, area, stroma, and S/A ratio for
each individual patient were calculated by adding the values
for each ovary and dividing by 2. For the echographic diagno-
sis of PCOS, we adapted the criteria of Adams to the quanti-
tative evaluation of stroma: a threshold value for S/A ratio of
0.34 (7) associated with ≥10 follicles with a diameter of 2–8
mm, arranged around an echodense central stroma (20),
has been considered to be positive for PCO.

After following a standard carbohydrate diet (300 g/d) for
3 days and fasting overnight for 10–12 hours, blood samples
were collected to perform the basal hormone assessment
(T, DHEAS, A, 17OH-P, P, FSH, LH, SHBG, PRL, cortisol,
E2, and IGF-I), serum lipid assays [triglycerides, total cholesterol, high- and low-density lipoproteins (HDL and LDL), very-low-density lipoprotein (VLDL), and nonesterified fatty acids (NEFA)], complete blood count, and hepatic and renal chemistries.

Patients then underwent an oral glucose tolerance test (OGTT). The OGTT was performed as follows. At 9:00 a.m. after overnight fasting, an indwelling catheter was inserted into the antecubital vein of one arm. Blood samples were collected basally, after ingestion of 75 g glucose in 150 mL water within 5 minutes and at 30, 60, 90, 120, 180, and 240 minutes. Insulin, glucose, and C peptide were assayed in all samples.

Plasma samples for glucose concentration were collected in tubes containing an inhibitor of glycolysis (sodium fluoride) to be analyzed within 5 hours. Plasma samples for insulin and C peptide concentrations were placed in tubes standing in ice, centrifuged for 10 minutes at 1,000g using a 4226 centrifuge (ALC, Milan, Italy), and kept frozen at 30°C until assayed.

**Study Design**

After the basal evaluation, patients were randomized to receive metformin (group A) or placebo (group B) for 6 months. Randomization was conducted using blocks of ten sealed opaque envelopes containing randomization codes assigning five patients to receive metformin and five patients to receive placebo. Fifteen patients were allocated to treatment with metformin, and 13 were allocated to treatment with placebo. Both participants and investigators were blinded to the treatment allocation, and randomization codes were not revealed until the last patient had completed the study protocol.

After the first evaluation visit, PCOS patients started the treatment with metformin at a dose of 500 mg twice a day, as previously described (21), or identical tablets of placebo in the same regimen. Patients were instructed to maintain a diet containing 25–30 kcal/kg body wt./day and moderate physical activity throughout the trial. After 3 and 6 months of treatment, on the third day of spontaneous or progestin-induced menstrual bleeding, patients returned to hospital and repeated the basal study.

On each visit, compliance with treatment was checked with a questionnaire about the side effects and a subjective evaluation of the tolerability of the administered drug; the patients were also asked if they had correctly followed the scheduled treatment, and all of them reported any missed administration. In group A (metformin), 13 patients completed the study therapy without major protocol violation regarding inclusion and exclusion criteria. Two patients were excluded from the study after 3 months for lack of compliance. In group B (placebo), 3 of the 13 women who were examined at baseline were lost to follow-up and were excluded from the data analysis.

**Measures**

All hormone assays were performed with commercial RIA kits (Radim, Rome, Italy). The intra- and interassay coefficients of variation for all hormones were <8% and <15%, respectively. For each determination, all samples from the same patient were assayed simultaneously.

Plasma glucose concentrations were determined by the glucose oxidase technique with a glucose analyzer (Beckman Coulter, Fullerton, CA). Total cholesterol and triglyceride concentrations were determined by an enzymatic assay (Bristol, Paris, France). The HDL concentrations were determined after precipitation of chylomicrons, VLDL, and LDL (Roche, Mannheim, Germany), and VLDL was separated (as the supernatant) from LDL and HDL by lipoprotein ultracentrifugation. A magnesium chloride/phosphotungstic acid technique was used to precipitate LDL from the bottom fraction after ultracentrifugation. All lipid assays were performed according to our standard laboratory procedures, as previously reported (15).

**Statistical Methods**

All results are presented as the mean ± SD. Insulin, C peptide, and glucose responses to the stimuli are also expressed as the area under the curve (AUC). The AUC was calculated by the trapezoidal rule method and reported as μIU/mL × 240 minutes for insulin and C peptide and as mg/dL × 240 minutes for glucose. The Kolmogorov-Smirnov test revealed that the data were not normally distributed. Data from the study groups were compared by using Mann-Whitney U test. The significance of differences between the same tests performed before and after treatment was assessed by using the nonparametric Wilcoxon rank sum test. Pearson correlation coefficient was used to define the correlation. A P value of <.05 was considered to be statistically significant.

**RESULTS**

Data analysis was limited to the subjects reporting a correct intake of the drug and who had completed the three evaluation visits planned by the study protocol.

The treatment was generally well tolerated; the most common adverse events either possibly or probably related to metformin were nausea and diarrhea in the first weeks of drug intake. No serious adverse events were related to metformin therapy.

None of the recruited women suffered from hypertension. Mean systolic and diastolic blood pressures remained stable during the treatment period. No alterations in plasma electrolytes were detected in the entire group throughout the study. We did not observe any pathologic modification of liver or renal parameters.

Main clinical and endocrine data of patients belonging to group A (metformin) and to group B (placebo) are shown in Table 1.
At baseline, 10 out of the 13 patients in group A and 7 out of the 10 patients in group B were oligoamenorrheic. All subjects presented a condition of mild to moderate hirsutism, with the exception of two patients in group A and one in group B, which presented a Ferriman-Gallwey score <8 at baseline. All the studied patients were normal weight (BMI <25 kg/m²) with a WHR <0.85. Ovarian and adrenal androgens levels were at the upper limit of or above the normal range. The two groups were well matched, with no statistically significant differences detected in clinical characteristics or in any of the above-mentioned parameters.

We did not observe any statistically significant modification in the anthropometric parameters in both group A and group B throughout the treatment period.

The majority of the studied patients in group A experienced an improvement in menstrual abnormalities, with a restoration of regular cycles in about 70% of patients after 6 months of metformin treatment compared with baseline (P<.01). At variance, no significant modifications in the menstrual pattern were reported by women allocated to group B.

Metformin therapy was able to induce a significant improvement of mean FG score, which reached statistical significance after 6 months of treatment (P<.05 for 6 months vs. baseline). Not unexpectedly, the placebo group did not show any change in this parameter.

No statistically significant modifications were observed in gonadotropins, E₂, and P levels during the 6 months of observation in both groups. A significant ameliorating effect on T levels was observed after 3 months (P<.05) and 6 months (P<.05) of metformin therapy. A significant decrease in 17OH-P levels was also obtained after 6 months in group A. Finally, we found in this group a decrease in DHEAS concentrations and in FAI, although such changes did not achieve statistical significance. Women treated with placebo did not exhibit changes in these values.

Sex hormone–binding globulin and A levels remained stable during the 6 months of treatment in both the groups.

Main metabolic characteristics of our patients are shown in Table 2. All of the patients showed a normal lipid profile, and no significant modifications were observed in total, LDL, or HDL cholesterol after both metformin and placebo treatment. At baseline, all participants presented normal glycemic and insulinemic responses to OGTT; no statistically significant modifications regarding AUC-insulin, AUC-glucose, and AUC-peptide were found in either group throughout the treatment period.

Regarding the ovarian ultrasound evaluation, at baseline we observed high ovarian volume, total ovarian area, stroma area, and mean S/A ratio in the studied patients, with no significant differences in the comparison between group A and B.

Metformin administration seemed to exert a positive effect on these features. After 6 months of insulin-sensitizing therapy, our data pointed toward a significant reduction in mean ovarian volume, which changed from the basal value of 14.6 cm³ to 9.6 cm³ (~34.2% decrease), and in S/A ratio, which changed from the mean value of 0.51 to 0.38 (~25.5% decrease) at the end of the treatment (Fig. 1). We observed a parallel decrease in T (~26% from pretreatment values) and in
Main metabolic features of the studied patients at baseline and after 3 and 6 months of metformin treatment (group A; n = 13) or placebo (group B; n = 10).

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<td>Total cholesterol (mg/dL)</td>
<td>151.1 ± 23.7</td>
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<td>LDL cholesterol (mg/dL)</td>
<td>92.9 ± 14.8</td>
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<td>HDL cholesterol (mg/dL)</td>
<td>49.6 ± 22.4</td>
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<td>NEFA (mEq/L)</td>
<td>0.38 ± 0.10</td>
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<td>TGL (mg/dL)</td>
<td>64.0 ± 22.4</td>
<td>70.2 ± 22.4</td>
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Note: AUC = Area under the curve; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NEFA = nonesterified fatty acids; TGL = triglycerides.

DISCUSSION

Earlier studies provided conflicting results about the effects of metformin in PCOS patients: some investigators upheld the theory of a beneficial impact of the drug on several aspects of the syndrome (8, 20, 22–24); in contrast, others failed to find substantial improvements (25). The studies with positive reports focus on moderately obese women, with an average BMI of <32 kg/m² (26–28); in contrast, when the effects of metformin administration were evaluated in massively obese subjects (BMI >39 kg/m²), the efficacy of the treatment was poor (25). Although the endocrine-metabolic ameliorations induced by metformin could be partly related to the parallel decrement in BMI, these modifications were similar in women who lost weight and in those who did not. As a consequence, it seems that some of the effects of metformin in PCOS could be independent of weight loss (29).

In accordance with this contention, Nestler reported that in nonobese PCOS patients, metformin may reduce serum insulin, which is one of the major stimulating signals of ovarian P450c17α activity, thus improving ovarian androgen synthesis and ameliorating the clinical symptoms of these women (26, 30). Actually, the advantage of metformin therapy was previously shown by other authors in normoinsulinemic overweight PCOS women, who obtained a restoration of normal menstrual cycles (31).

The present study pointed the attention properly on the effect of metformin in normal-weight PCOS patients, which represent about 30% of affected women. The results seem to suggest an interesting possible new mode of action for an old therapy.

Up to 75% of the metformin-treated PCOS women experienced a restoration of menstrual cyclicity in the absence of any significant modification in BMI, WHR, or glucoinsulinemic and lipid profiles, which were already normal at baseline, in accordance with the study design. In contrast, the placebo-treated group did not undergo any apparent clinical improvement of ovarian function.

We intentionally chose to recruit a highly selected population of normal-weight and normoinsulinemic PCOS patients to exclude all of the the factors with a potential confounding role: although there is no doubt that metabolic disruption may play a paramount role in the pathogenesis of the endocrine-reproductive imbalance of most PCOS patients, we hypothesized that, in the absence of any metabolic signs, a more strictly intraovarian mechanism might be predominant. How metformin could affect this defect is the intriguing question we attempted to answer.
An interesting clue could be provided by the most typical clinical feature that normal-weight PCOS patients share with the rest of the PCOS population: the appearance of the ovary. In the past years, the diagnostic relevance of the ovarian morphology encountered varying assent in the scientific community, and, to date, there is not a general agreement on which ovarian characteristic, if any, may be related to the complex clinical picture of PCOS.

Some authors suggested that precise ultrasound measurements could improve the detection of ovarian androgenic dysfunction, thus representing a complementary finding in the diagnosis of PCOS (32, 33). In fact, ovarian stromal hypertrophy frequently and specifically reveals the state of hyperandrogenism. Elevated plasma androgen levels of ovarian origin represent the endocrine feature more closely related to the increased ovarian stroma and volume. However, elevated serum immunoreactive LH levels are not constantly linked to the ultrasound appearance of the ovary (32).

The recent Rotterdam Consensus (12) rehabilitated the role of ultrasound in the diagnosis of PCOS, even if the description of the distribution of follicles and stroma characteristics is not required for the diagnosis. It is well known that an increased stromal echogenicity and/or stromal volume are specific to PCOS, although their exact measurement is difficult in the clinical routine. We previously demonstrated that the assessment of ovarian volume (or area) could be considered to be a good surrogate for the quantification of the stroma in clinical practice (6, 34).

In a recently published study on a population of 375 PCOS women conducted by our group, we found that the S/A ratio was significantly related to T, A, and 170H-P plasma levels as well as to FAI values. Moreover, this ultrasonographic parameter was able to identify individuals with more pronounced androgen abnormalities (35).

In the present study, the finding of basal high ovarian volume, area, stroma, and mean S/A ratio in PCOS women confirm the literature reports for the diagnosis of polycystic ovaries. The novel acquisition is the observation of a significant reduction of ovarian volume and S/A ratio after 6 months of metformin administration.

This is the first study documenting a modification in the ovarian structure in relation to long-term metformin administration. This finding is in keeping with a recent study on the acute effect of metformin administration on the ovarian morphology in PCOS: a 7-day course of metformin administration was demonstrated to be able to significantly decrease the antral follicular count in a group of PCOS women with heterogeneous metabolic features (35).

Earlier studies evaluating obese or overweight PCOS patients suggested the possibility of a relationship between ovarian morphology and anthropometric characteristics (7, 32). In contrast, in the present study the S/A ratio did not correlate with BMI, probably because all of the patients were normal weight, and no modifications were observed in the anthropometric characteristics after the 6 months of treatment. Furthermore, the significant decrease in total ovarian volume and in S/A ratio occurred in the absence of glucoinsulinemic changes.

More relevant to the interpretation of our data, a number of reports in the literature have noted the association between some ultrasound ovarian characteristics and the androgenic milieu (33, 36–38). In accordance with this evidence, the concomitancy between the modifications in the ovarian volume and, in particular, S/A ratio and the changes in androgens levels found in 10 out of the 13 metformin-treated PCOS subjects seems to further underscore the link between the androgenic assessment and such ovarian features. Unfortunately, we were not able to find a significant correlation between these two parameters, probably owing to the relatively small sample under evaluation.

The mechanism through which metformin may succeed in decreasing androgen levels in PCOS is complex and not fully clarified (39). The most widely accepted theory is that metformin could be able to improve hyperandrogenism in PCOS by reducing circulating insulin levels by stimulating SHBG production and modulating LH discharge.
Nevertheless, in most studies, the insulin-lowering action of the drug seems not to be reliable enough to explain the reported hormonal and clinical changes. This evidence is most relevant in PCOS women with normal basal glucocinsulinemic metabolism. The mechanism candidate for clarifying such discrepancy could be the ability of metformin to directly act on the gonad. In such a perspective, an earlier in vitro study demonstrated that metformin may display a direct inhibitory action on A and T production by human ovarian theca-like tumor cells (40). This effect seems to be mediated through the reduced expression of steroidogenic acute regulatory protein, which is considered to be the rate-limiting step in steroid hormone production in the gonads. More recently, Mansfield et al. (41) confirmed a decrease in A production by theca cells from pooled follicles incubated in the presence of metformin, and, interestingly, this effect was dose-dependent. Although the concentration of the drug that follicular cells are exposed to in women on oral metformin treatment are unknown, those investigators were able to detect changes in in vitro steroidogenic activity with doses (10^12 mol/L) which might be expected to be at or below the range reached in vivo (41).

Beyond the peripheral beneficial consequences, the decrease in intraovarian androgen concentrations may have a role in the improvement of ovulatory function and menstrual cyclicity observed in this and other studies (8, 9, 11, 21). Folliculogenesis is typically disturbed in PCOS: the selection process does not occur and follicular growth undergoes a premature arrest, leading to the accumulation of small antral follicles in the gonad. The putative pathophysiological explanations involve both intra- and extravascular regulators of ovulation: the intraovarian hyperandrogenism is believed to promote early follicular growth, leading to a 2–5-mm follicle excess; the impairment in the modulation of granulosa cell proliferation and apoptosis, which are under the control of local ovarian growth factors, such as IGF-I and insulin, is likely to intervene; extravascular factors, such as LH and insulin excess, may have a worsening effect per se and by amplifying the other mechanisms (42).

Therefore, it has been suggested that the effect of metformin on the ovary may not be limited to the hormonal synthesis, but may also involve granulosa cell viability through the direct modulation of differential enzymatic pathways (43). Intriguingly, preincubation with metformin seems able to reduce the susceptibility of cultured granulosa cells to undergo apoptosis.

All of these studies provide potential molecular mechanisms for the improvement of follicular growth patterns and androgen synthesis due to metformin treatment, independently of metabolic changes. Thus, it could be postulated that the changes in ultrasonographic ovarian features, along with the improvement in androgen milieu and the resumption of menstrual cyclicity in the majority of our metformin-treated patients, could be the consequence of an amelioration in ovulatory function.

In conclusion, the present data seem to confirm the therapeutic role of metformin in normal-weight normoinsulinemic PCOS women: this drug was shown to restore the menstrual pattern and to improve the hormonal milieu with a mechanism that, albeit not fully clarified, seems to be insulin independent and instead targeted to the ovary itself.

Further studies are needed to elucidate the specific mechanism of action of metformin in normal-weight PCOS patients, opening the field to new lines of treatment for this particular group of PCOS women, with very interesting potential implications for the management of anovulatory infertility.

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