An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate–metformin in patients with polycystic ovary syndrome

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Objective: To compare the effect of clomiphene citrate, metformin, and lifestyle modification on treatment of patients with polycystic ovary syndrome (PCOS).
Design: Prospective randomized double-blind study.
Setting: University-based infertility clinic and research center.
Patient(s): Three hundred forty-three overweight infertile women with PCOS.
Intervention(s): The participating women were assigned to four groups: clomiphene (n = 90), metformin (n = 90), clomiphene + metformin (n = 88), and lifestyle modification (n = 75). The patients in each group received standardized dietary and exercise advice from a dietitian.
Main Outcome Measure(s): The primary outcome variables were change in menstrual cycle, waist circumference measurements, endocrine parameters, and lipid profile. The main secondary outcome variable was clinical pregnancy rate.
Result(s): The clinical pregnancy rate was 12.2% in clomiphene group, 14.4% in metformin group, 14.8% in clomiphene + metformin group, and 20% in lifestyle modification group. Lifestyle modification group achieved a significant reduction in waist circumference, total androgen, and lipid profile.
Conclusion(s): Lifestyle modification improves the lipid profile in PCOS patients. Therefore, lifestyle modification may be used as the first line of ovulation induction in PCOS patients. (Fertil Steril¬ 2010;94:216–20. ©2010 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, clomiphene, metformin, lifestyle modification, ovulation induction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies, affecting 5%–10% of women at a reproductive age (1). Women with PCOS are characterized by any of oligoovulation, clinical or biochemical hyperandrogenism, and polycystic ovaries (2, 3). Women most commonly seek counseling or treatment because of infertility related to ovulation (4). It is a heterogeneous syndrome both in its clinical presentation and in its laboratory manifestation (5, 6). The main disturbances in this syndrome are abnormal ovarian morphology, abnormal steroidogenesis, hyperinsulinemia present in about 80% of obese women, and abnormal gonadotropin secretion (7, 8). One of the major biochemical features of PCOS is insulin resistance followed by compensatory hyperinsulinemia (9, 10). The rate of insulin resistance in women with PCOS is 50%–80% and a large majority of them are obese (11). Recent data show that hyperinsulinemia produces hyperandrogenism in PCOS by increasing ovarian androgen production and decreasing serum SHBG concentration (12, 13).

Received October 22, 2008; revised February 12, 2009; accepted February 25, 2009; published online May 21, 2009.
M.A.K. has nothing to disclose. M.J. has nothing to disclose.
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High levels of androgenic hormones interfere with the pituitary-ovaries axis, leading to increased LH levels, anovulation, amenorrhea, and infertility (14). The ideal treatment for obesity and hyperinsulinemia is reduction of insulin resistance. This is the primary goal in cases with PCOS (15). Curiously, in obese females with PCOS, a loss of just 5%–10% of body weight is enough to restore the reproductive function by 55%–100% within 6 months (16). Clomiphene citrate (CC) has long been the first line of treatment for those with oligo- or anovulation. Clomiphene citrate acts within the brain to promote the production of GnRH. As a result, the pituitary gland makes FSH and LH, the hormones that stimulate ovarian function (1).

A duration of three to six ovulatory cycles is usually sufficient to know whether pregnancy will be achieved using CC before moving on to a more complex treatment, because about 75% of the pregnancies achieved with clomiphene occur within the first three cycles of treatment (16). The main factors that predict outcome of treatment are obesity, hyperandrogenemia, elevated testosterone concentrations, severe insulin resistance, and age (17). The discrepancy between ovulation and pregnancy rates may be partly explained by the peripheral antiestrogenic effects of CC at the level of the endometrium and cervical mucus or by hypersecretion of LH (18).

0015-0282/$36.00
doi:10.1016/j.fertnstert.2009.02.078

Around 20%–25% of anovulatory women with PCOS do not respond to CC and are considered to be "clomiphene resistant" (19). Failure to ovulate or get pregnant with CC may be due to hyperinsulinemia, which may contribute to hyperandrogenism. Some agents may be used for amelioration of insulin resistance and reduction of circulating insulin level. Metformin is the most extensively studied insulin-lowering agent in the treatment of PCOS (20). The basic etiology of the anovulation associated with PCOS is mainly insulin resistance and hyperinsulinemia (21, 22). Data have shown that insulin resistance has an important implication in the pathogenesis of PCOS and that insulin-sensitizing drugs are an effective therapeutic approach. (1).

The indications for the administration of metformin to anovulatory women with PCOS in an ovulation-induction program have widened, so that it seems to be difficult to predict which individuals will respond well to this medication (22). At present, use of metformin in PCOS should be restricted to those patients with glucose intolerance (23), and so it alone is less effective than CC in inducing ovulation in women with PCOS. There seems to be no advantage to adding metformin to CC in PCOS patients.

Lifestyle modification programs with an emphasis on behavioral management and dietary and exercise interventions have been successful in improving reproductive and metabolic features in PCOS, although as yet there is limited evidence for specific dietary and exercise approaches and guidelines for use in PCOS (24). Lifestyle modification may be best defined as a change of behavior and correction of wrong eating habits. Weight loss occurs when energy expenditure exceeds energy intake (24). Physical activity is an important component of any weight management program. Although energy restriction by dieting is largely responsible for initial weight loss, regular physical activity helps to maintain weight loss and prevent weight regain. Lifestyle change is an important therapeutic strategy in all overweight or obese patients with PCOS (24).

Therefore, in the present study, the primary approach for achieving weight loss was therapeutic lifestyle modification which included a reduction in energy intake and an increase in physical activity. The aim of this study was to compare the lifestyle modification with medical treatment of PCOS patients using clomiphene, metformin, and clomiphene + metformin.

MATERIALS AND METHODS

Three hundred forty-three infertile women were included in the patients attending the outpatient clinic of the Infertility Research Center of Yazd Medical University. The present study was approved by the Institutional Review Board at Yazd University of Medical Science. The diagnosis of PCOS was based on European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine guidelines (Rotterdam criteria, 2003), as including at least two of the following three criteria: 1) chronic anovulation; 2) clinical or biochemical signs of hyperandrogenism; and 3) polycystic ovary morphology shown on ultrasound scan, defined as the presence of ≥ 12 follicles (with one ovary being sufficient for diagnosis) measuring 2–9 mm in diameter. No patient showed hyperprolactinemia, clinical evidence of hypercorticism, or thyroid, liver, or kidney dysfunction. Our inclusion criteria were: 1) age between 19 and 35 years (body mass index [BMI] 25–29.9 kg/m^2) with primary infertility with PCOS; 2) normal thyroid, liver, and kidney function; 3) serum level of PRL within normal levels; 4) fewer than six menstruation cycles per year; 5) taking no metformin in pervious 8 weeks for ovulation induction; 6) serum hCG within normal levels; and 7) spouse with a sperm concentration of ≥ 20 million/mL, motility >50%, morphology >30% (World Health Organization criteria).

Study Groups

Patients who were eligible and consented were randomly assigned to four groups consisting of CC, metformin, CC and metformin, and lifestyle modification.

The patients randomized to CC were given only CC at a dose of 100 mg on days 3–7. Transvaginal sonography and follicular tracking were done. If there was evidence of ovulation but the patient did not get pregnant, the same dosage was continued for a maximum of three to six cycles. The patients randomized to the metformin group were given the tablets at the initial dose of 500 mg, which was increased in a stepwise manner during the first 3 weeks to accommodate the side effects until the patients were taking a total of 1,500 mg/day (for 3–6 months). In the combination treatment group, metformin and CC were given in a similar manner.

All of the patients in the study group referred to dietitians received the following pieces of advice regarding their diets and exercise program:

A. For an appropriate weight loss, there should be a low-calorie diet, 500 caleries less than daily requirements, including 50%–60% carbohydrates, 25%–30% fat, and 15%–20% of proteins.
B. To ensure risk-free exercise, all the moves should be taken in controlled conditions and under careful monitoring. Moreover, they should be performed in accordance with the prescribed rehabilitation menu.

Generally speaking, an average of 30 minutes of exercise everyday, such as climbing up steps or simply walking, proves to be useful. It is not aerobic alone to be recommended. Rather, strength training, too, serves as an important part of a program leading to the reduction of the fatty mass in the body. The exercises should be taken three to five times a week regularly, each time for 20–60 minutes. Their intensity should be adjusted to the subject's heart beat.

Study Measurements

All of the samples were assessed before and 6 months after the beginning of the study for: BMI, 2-hour postprandial

TABLE 1

Baseline characteristics of the subjects in clomiphene, metformin, clomiphene + metformin, and lifestyle modification groups.

	Clomiphene citrate		Metformin		Clomiphene + metformin		Lifestyle modification	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age, y	27.47	2.38	27.33	2.34	27.34	2.27	27.48	2.69
Infertility period, y	4.1	1.07	3.9	0.89	4.55	1.20	3.90	0.98
BMI, kg/m^2	27.20	2.93	27.17	1.73	27.96	1.14	27.92	1.05
HDL, mg/dl	41.46	4.57	45.01	6.10	36.73	5.36	39.40	4.40
LDL, mg/dl	190.42	66.17	196.31	61.73	137.78	50.10	223.76	80.00
T, mg/dl	0.8	0.24	0.7	0.29	0.9	0.33	0.8	0.22
FBS, mg/dl	100.3	8.19	101.01	8.38	93.09	10.07	122.85	78.95
2HPP, mg/dl	114.74	6.41	129.22	31.37	74.12	36.23	85.01	25.6
SHBG, mg/dl	35.62	10.86	27.58	7.12	61.12	37.53	48.08	72.97
Waist circumference, cm	102.16	6.31	102.11	4.74	97.38	12.15	98.62	73.3

Note: 2HPP = 2-hour postprandial glucose; BMI = body mass index; FBS = fasting blood sugar; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

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glucose, fasting blood sugar, low-density lipoprotein (LDL), high-density lipoprotein (HDL), testosterone (T), SHBG, β-hCG after 7 days of retardation of menses, and abdominal ultrasound for detection of fetal heart.

Statistical Analysis

All of the data were processed by SPSS software version 14.0 (SPSS, Chicago, IL) and analyzed with Fisher exact test, chi-squared test, and analysis of variance test (ANOVA). A P level of $<.05$ was considered to be significant.

RESULTS

The present study was designed to compare lifestyle modification with medical treatments clomiphene, metformin, and clomiphene + metformin of patients with PCOS. A total of 343 women with PCOS were selected by the Rotterdam criteria and followed-up in four groups—clomiphene (n = 90), clomiphene + metformin (n = 88), metformin (n = 90), and lifestyle modification (n= 75)—in an 8-month period. There were no significant differences in the basic variables among the four groups before the study began. The mean ages in the groups—clomiphene (27.47 ± 2.38 yrs), metformin (27.33 ± 2.34 yrs), clomiphene + metformin (27.43 ± 2.27 yrs), and lifestyle modification (27.84 ± 2.69 yrs)—showed no significant difference from one another (P=.9). The infertility periods in the clomiphene (4.7 ± 1.07 yrs), clomiphene + metformin (4.5 ± 1.00 yrs), metformin (3.90 ± 0.98 yrs), and lifestyle modification (3.92 ± 0.89 yrs) groups were not significantly different (P=.1; Table 1).

The improvement rates of menstrual cycle in the clomiphene (66.6%), clomiphene + metformin (62.5%), metformin (55.5%), and lifestyle modification (66.6%) groups were not significantly different (P=.38).

Clinical pregnancy rates in the clomiphene (12.2%), metformin (14.4%), clomiphene + metformin (14.8%), and lifestyle modification (20%) groups showed no significant difference from one another (P=.56; Table 2).

Multiple pregnancy rates in the clomiphene (2.2%) and clomiphene + metformin groups (1.1%) were not significantly different from each other (P=.3). There were no multiple pregnancies seen in the metformin and lifestyle modification groups.

TABLE 2

Pregnancy rate in clomiphene, metformin, clomiphene + metformin, and lifestyle modification groups.

Pregnancy	Clomiphene	Clomiphene + metformin	Metformin	Lifestyle modification
Positive	11 (12.2%)	13 (14.4%)	13 (14.4%)	15 (20%)
Negative	79 (87.8%)	75 (85.2%)	77 (85.6%)	60 (80%)
Total	90	88	90	75

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The waist circumference of the women who were included in the study was significantly lower after the treatment plan in the lifestyle modification group compared with the other three groups (P=.001). Insulin and LDL levels in the lifestyle modification group showed significant difference compared with the other three groups ($P \leq .05$). Improvement of SHBG in the lifestyle modification and metformin groups showed significant differences compared with the other two groups ($P \leq .05$).

DISCUSSION

This study compared lifestyle modification with medical treatment plans such as clomiphene, metformin, and clomiphene + metformin in women who had PCOS. A total of 343 women with PCOS were selected and followed-up in four groups for an 8-month period. Before the study began, there were not any significant differences in basic variables among the four study groups. The findings do not support the hypothesis that CC and metformin either alone or in combination together improve the rate of clinical pregnancy in PCOS women. However, LDL, T, and SHBG changes were significantly improved in the lifestyle modification group compared with the others. The rate of menstrual cycle improvement and clinical and multiple pregnancies in the lifestyle modification group were not significantly higher than in the other three study groups. Waist circumference, serum level of insulin, LDL and SHBG in the lifestyle modification group showed significant differences from those in the medical treatment groups (the other three study groups) after starting the treatment plan.

In the present study, all of the women had to have a 5% weight loss before they were included in the study. In other words, $\geq$5% weight loss was needed for starting menstrual cycles. According to Clark et al. (22), 6 months after calorie restriction, pregnancy was achieved in 50% of women with PCOS. In that same earlier study, as in the present study, lifestyle modification and weight loss can cause improvements in menstrual cycles, ovulation, and metabolic and hormonal status of PCOS women. Pelchlivanov et al. (25) assessed biochemical and hormonal changes in PCOS women who were treated with metformin and CC. They believed that only weight loss can cause an improvement in biochemical and hormonal status and spontaneously restore menstrual cycles in women. Qublan et al. (26), comparing the effect of weight loss and of metformin on fertility function in PCOS women, reported that both of them can be used to achieve this goal.

In the present study, LDL, T, and SHBG changes showed significant differences between the lifestyle modification group and the other three groups. Also, Harborne et al. (27) reported that metformin can cause a weight loss in PCOS women.

In the present study, the pregnancy rate in the metformin + clomiphene group was lower than that in the lifestyle modification group but higher than metformin or clomiphene alone groups. Legro et al. (19) showed that PCOS women who were treated with a combination therapy of metformin and clomiphene had a pregnancy rate higher than with each of them alone. In their survey, Moll et al. (28) had a different idea. They indicated that adding metformin to clomiphene does not increase pregnancy rate and that clomiphene is the first line of treatment in PCOS women.

Tan et al. (29) reported that metformin can improve the metabolic status of PCOS women. Women that were treated with metformin in the present study had no differences in their BMI from the other three groups. A similar meta-analysis (30) reported that metformin can cause ovulation induction and decrease fasting insulin and LDL cholesterol but has no effect on BMI or waist circumference. In the present study, serum LDL, insulin, and SHBG changes in the women in the lifestyle modification group were significantly different from those of the other three groups. Orio et al. (31), in their study of 30 women with PCOS over 5 months, got similar results and reported that weight loss after 4–12 weeks causes a significant improvement in their endocrine and metabolic parameters. In Kiddy et al.'s study, the improvement of endocrine and metabolic parameters was achieved after 10 weeks of dietary regimen (32). Hamilton-Fairley et al. (33) believed that an increase in the serum level of SHBG with a decrease in free T and fasting insulin were the specific characteristics of a treatment plan for PCOS women on dietary regimen and physical exercises. Tang et al. (34) showed that metformin, unlike lifestyle modification, could not cause weight loss or restore spontaneous menstrual cycles.

CONCLUSIONS

The results of the present study show that metformin or metformin with clomiphene does not cause a significant weight loss or an improvement in the endocrine status of PCOS women. However, lifestyle modification can improve their menstrual cycles and hormonal status. Regarding the side effects of medical treatment for PCOS, such as hyperinsulinemia, hyperanderogenemia, and cardiovascular disorders, lifestyle modification proves to be the first and foremost way of dealing with the problem.

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