

Dietary intervention versus metformin to improve the reproductive outcome in women with polycystic ovary syndrome

A prospective comparative study

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ABSTRACT

Objective: To compare the clinical results and reproductive outcome in obese women with polycystic ovary syndrome (PCOS) following dietary intervention or treatment with metformin.

Methods: Forty-six patients with PCOS were studied prospectively in Prince Rashed Hospital, Irbid, Jordan, between January 2003 and April 2005. The women were randomly divided into 2 groups: Group 1 (n=24) was prescribed with 1200-1400 kcal/day diet (25% proteins, 25% fat, and 50% carbohydrates plus 25-30 gm of fiber per week). Group 2 (n=22) was assigned to take 850 mg of metformin twice in a continuous manner. Both treatments continued for 6 months. Clinical and biochemical data, before and after both treatments along with the reproductive outcome were compared between the 2 groups.

Results: There were no significant differences between the 2 groups in terms of age, body mass index (BMI) and duration of infertility. Both groups had a significant improvement after treatment in the menstrual cyclicality (66.7% and 68.2% versus 12.5% and 18.2%) and significant reduction in BMI (mean of 27.4 and 27.8 versus 32.2 and 31.9), luteinizing hormone levels (7.9 ± 1.7 and 6.9 ± 1.8 versus 11.8 ± 2.2 and 11.5 ± 1.8), and androgen (testosterone, androstenedione, dehydroepiandrosterone sulfate) concentration. The clinical, biochemical, and reproductive outcome including menstrual cycle pattern, ovulation, and pregnancy rates were similar in both groups after treatment.

Conclusion: Amelioration of hyperinsulinemia and hyperandrogenemia with dietary intervention or metformin treatment improves significantly the clinical features and reproductive function in overweight PCOS women.

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Polycystic ovary syndrome (PCOS) is a heterogeneous disorder that characterized by hyperinsulinemia with insulin resistance and hyperandrogenemia.¹ Most of the manifestations of this syndrome including menstrual irregularities, hirsutism and chronic anovulation are related to the hyperandrogenic status found in these women.² Approximately 50% of women with PCOS are overweight or obese.¹⁻⁴ Insulin resistance is most commonly found in obese PCOS women (65%), but can also demonstrated in nearly 20% of lean PCOS women.¹ It has been suggested that the resulting hyperinsulinemia augments the LH-driven production of androgens from the ovarian theca cells in these women.⁵ The association between PCOS-related hyperandrogenemia and insulin resistance is well documented.^{1,5-8} It has been reported that hyperinsulinemia with insulin resistance is more profound in obese than lean women with PCOS.^{1,9} In obese women with PCOS, usually the reproductive disorders are more prevalent. It has been suggested that the body mass index (BMI) contributes significantly towards the severity of these problems.⁹ By understanding, hyperinsulinemia is the underlying pathogenetic mechanism. Several studies showed that weight loss and the use of insulin sensitizing drugs such as metformin can ameliorate the insulin resistance, improving significantly the reproductive outcome in these women.¹⁰⁻²¹ We conducted this prospective study to compare the clinical results and reproductive outcome in obese women with PCOS following diet or treatment with metformin.

Methods. Forty-six patients with PCOS were studied prospectively in Prince Rashed Hospital

(PRH), Irbid, Jordan, between January 2003 and April 2005. The PCOS was diagnosed based on the clinical, laboratory and ultrasonographic criteria according to the consensus criteria reported by the Rotterdam European Society of Human Reproduction and Embryology (ESHRE)/ American Society of Reproductive Medicine (ASRAM) workshop group.²¹ These include 1. Oligo- or anovulation 2. Clinical (oligo- or amenorrhea) and biochemical signs of hyperandrogenism [increased LH and total serum testosterone (T) levels] and 3. the presence of polycystic ovaries on vaginal ultrasonography (presence of ≥ 12 follicles in each ovary measuring 2-0 mm in diameter, and - ovarian volume >10 ml). Congenital adrenal hyperplasia, cushing's syndrome, hyperprolactinemia and thyroid disease were excluded by appropriate tests. Liver and kidney function tests were all normal. Selection criteria were aged <36 years; duration of infertility >2 years; BMI >29 kg/m², and patients who are clomiphene citrate-resistant (defined as failure to ovulate after clomiphene citrate-treatment up to a daily dose of 150 mg from cycle day 5-9 for at least 3 consecutive cycles. All patients were required to have normal uterine cavity and tubal patency on hysterosalpingography. All male partners had normal semen parameters according to the World Health Organization criteria. Ultrasonographic examination was performed on days 3-5 of a spontaneous or induced progestin cycles to measure the ovarian volume and the number of microfollicles. All ultrasound examinations were carried out transvaginally. Body mass index was calculated as weight (kg) divided by height (m) squared. Twenty-four women (Group I) were prescribed a 1200-1400 K Cal. The patients were selected randomly and divided into 2 groups. Randomization was accomplished using a selection from a table of random numbers available in the standard statistics textbook kcal/day diet¹² (25% proteins, 25% fat, and 50% carbohydrates plus 25-30 gm of fiber per week). Weight assessment was carried out every 4 weeks. Twenty-two women (Group II) were assigned to take 850 mg of metformin (Glucophage: Lipha Sante, Lyon, France) twice a day in a continuous manner. Both treatments were continued until the patient resume the first regular cycle (defined as the first cycle to occur 24-35 days after treatment). When this occurs, serum progesterone was assayed on day 21 and 28 of the cycle. The progesterone level >10 ng/ml was indicative of ovulation. Women who did not menstruate within 2 weeks of a serum progesterone >10 ng/ml, were assessed for urine pregnancy testing or serum beta-human chorionic gonadotropin measurement. If there were no resumption of regular cycle and no evidence of ovulation, both treatments were continued for 6 months. The duration of follow-up was 12 months. Pre-treatment clinical and hormonal

data were compared with those treated after between the 2 study groups. Blood samples were drawn on day 3 or 4 of the menstrual cycle or progesterone-induced bleeding before commencing both treatment and repeated after 6 months. Blood samples were allowed to clot at room temperature, and the serum was separated and frozen at -20°C until assay. Radioimmunoassay was used to measure free testosterone (normal range [nr]: 65-119 ng/ml), dehydroepiandrosterone sulfate (DHEAS) (nr: 80-560 $\mu\text{g/dl}$), androstenedione (nr: 0.5-3.0 ng/mL), 17-hydroxyprogesterone (17-OHP) (nr: 0.4-3.3 $\mu\text{g/dl}$) and progesterone (Diagnostic Product, Corporation, USA). Fluoroimmunoassay was used to measure LH (nr: 0.7-6.2 mIU/ml), follicle stimulating hormone (FSH) (nr: 3.3-8.8 mIU/ml) (DPC, USA), and serum insulin (Abbot, USA). Serum glucose was determined by the glucose oxidase method (Randox, UK).

Informed consent was obtained from all women and the study protocol was approved by the Scientific Committee of the Department of Obstetrics and Gynecology. Chi-square test, and student-t test were used to analyze differences between the 2 groups. A p -value of <0.05 was considered statistically significant. Data were entered using the statistical Package for Social Sciences (Chicago, IL) software, version 10 and Microsoft EXCEL software (Microsoft, Redmond, WA).

Results. Demographic data of 46 obese infertile women with PCOS are summarized in **Table 1**. Twenty-four women were assigned for diet (Group I). There were no significant differences between the 2 groups in terms of age, BMI and duration of infertility. **Table 2** shows the clinical, biochemical, hormonal data of the 2 groups before and after treatment. Before starting treatment, there were no significant differences between the 2 groups in terms of BMI, menstrual cycle pattern, hirsutism, hormonal levels [testosterone, androstenedione, DHEAS, 17-OHP, LH, FSH, E2, insulin] and fasting glucose levels. Similarly, the menstrual cycle pattern, hormonal and glucose levels showed no significant differences between the 2 groups after treatment. When the results after treatment compared to those before treatment, both groups had significant improvement in the menstrual cyclicity (66.7% and 68.2% versus 12.5% and 18.2%) and significant reduction in BMI (mean of 27.4 and 27.8 versus 32.2 and 31.9), LH levels (7.9 ± 1.7 and 6.9 ± 1.8 versus 11.8 ± 2.2 and 11.5 ± 1.8) and androgen (T, androstenedione, DHEAS) concentration. On the other hand, there were no significant in the hirsutism, levels of FSH, 17-OHP, fasting insulin and glucose. Menstrual and reproductive outcome over 6-month period is shown in **Table 3**. Thirteen of 21

Table 1 - Demographic data of both groups.

Demographic data	Weight reduction n=24	Metformin treatment n=22	P-value
Age (range)	31.5 (19-38)	30.8 (20-37)	Not significant
Body mass index (kg/m ²)	32.2 (29-43)	31.9 (29-44)	Not significant
Duration of infertility (year)	5.4	5.2	Not significant

Table 2 - Clinical, biochemical, hormonal, and reproductive data of both groups before and after treatment.

Parameters	Weight reduction n=24		Metformin treatment n=22		P-value
	Before	After	Before	After	
Body mass index (range)	32.2 (29-43)	27.4	31.9 (29-44)	27.8	<0.01
<i>Menstrual cycle (%)</i>					
Regular	3 (12.5)	16 (66.7)	4 (18.2)	15 (68.2)	<0.01
Irregular	21 (87.5)	9 (37.5)	18 (81.8)	7 (31.8)	
Hirsutism (%)	15 (62.5)	13 (54.2)	16 (72.7)	13 (59.1)	NS
<i>Hormonal profile (mean±SD)</i>					
T (ng/ml)	329 ± 49	207 ± 31	336 ± 38	198 ± 29	<0.01
Androstenedione (ng/ml)	3 ± 0.7	1.8 ± 1.1	3 ± 0.8	1.9 ± 0.7	<0.05
DHEAS (µg/dl)	253 ± 32	159 ± 31	250 ± 28	162 ± 27	<0.05
17-OHP (µg/dl)	1.5 ± 0.2	1.4 ± 0.3	1.5 ± 0.6	1.5 ± 0.2	Not significant
LH (mIU/ml)	11.8 ± 2.2	7.9 ± 1.7	11.5 ± 1.8	6.9 ± 1.8	<0.05
FSH (mIU/ml)	6.6 ± 0.9	5.5 ± 1.4	5.8 ± 1.8	5.2 ± 1.4	Not significant
LH:FSH ratio	2.6 ± 0.3	1.4 ± 0.2	2.6 ± 0.4	1.5 ± 0.3	<0.05
Fasting glucose (mg/dl)	83 ± 3.6	81.6 ± 5.1	82 ± 4.3	80.2 ± 4.2	Not significant
Fasting insulin (µU/ml)	16 ± 3.8	14.5 ± 2.4	17 ± 3.7	15.4 ± 2.6	Not significant
Serum Estradiol level (pg/mL)	48 ± 5.1	45 ± 3.8	47 ± 4.5	46 ± 3.8	Not significant

DHEAS - dehydroepiandrosterone sulfate, 17-OHP - 17-hydroxyprogesterone, FSH - follicle stimulating hormone

Table 3 - Menstrual and reproductive outcome of both groups.

Outcome	Weight reduction n=24	Metformin treatment n=22	P-value
Resumption of regular cycles (%)	13/21 (61.9)	11/18 (61.1)	Not significant
<i>Ovulation rate (%)</i>			
Spontaneous	12/24 (50.0)	0/22 (45.5)	Not significant
With clomiphene citrate	8/12 (66.7)	6/10 (60.0)	Not significant
With clomiphene citrate	4/12 (37.3)	4/10 (40.0)	Not significant
<i>Pregnancy rate (%)</i>			
Multiple pregnancy	8/24 (33.3)	6/22 (27.3)	Not significant
Multiple pregnancy	1/8 (12.5)	1 (16.6)	Not significant
Abortion rate	1/8 (12.5)	1/6 (16.7)	Not significant

women (61.9%) in the diet group who had irregular menses, resumed regular cycles compared to 11 of 18 (61.1%) in the metformin treated group. This difference was not statistically significant. Furthermore, there were no significant differences between the 2 groups after treatment in the ovulation and pregnancy rates. Twelve women in the diet group had ovulation of whom 8 had spontaneous and 4 with clomiphene citrate-induced ovulation. Eight of these women conceived of whom one had first trimester abortion. On the other hand, 45.5% (10/22) of the women in the metformin treated group had ovulation (spontaneous in 6 and clomiphene citrate-induced in 4) of whom 6 women conceived. Abortion occurred in one case. Five women (20.8%) in the metformin treated group complained of diarrhea of 2-3 weeks duration after resumption of treatment that resolved without intervention.

Discussion. The results of our study showed that weight loss after diet or metformin treatment was associated with significant improvement in the clinical and hormonal characteristics of women with PCOS. This improvement was reflected clearly with the improved reproductive outcome. Our data showed that women in the diet group had weight loss of 5-17% of their initial weight with a mean of 8.5% over 6-month period (data not shown). A significant reduction in the androgen levels along with significant improvement in the menstrual cyclicity and reproductive function was observed in this group. These findings are consistent with those reported previously. Crosignani et al¹³ studied 27 anovulatory overweight patients with PCOS after prescribing a 1200 kcal/day diet for 6 months. Eighteen of their patients resumed regular menses and spontaneous ovulation in 15 women and pregnancy occurred in 10 women. Authors concluded that the improvement of anthropometric indices in obese PCOS patients induced by weight loss reduces the ovarian volume and microfollicle number with subsequent improvement of the reproductive outcome. Moreover, evaluating 28 overweight PCOS women, Moran et al¹⁵ reported significant decrease in terms of BMI, androgen levels, insulin resistance, and fasting insulin. The menstrual cyclicity and reproductive outcome improved significantly after a 12-week prescribed diet. In a more recent study, Moran et al¹⁶ prescribed a short-term energy restriction for 8 weeks for 34 overweight PCOS women report similar findings. The effect of weight loss on reproductive function depends on the amount of weight loss. It has been reported that weight losses 2-10% of the initial body weight can ameliorate the hyperinsulinemia and hyperandrogenemia that

observed in obese PCOS women.^{17,18} In our study, the mean body loss was 8.5% of the initial body weight. This agreement with the former studies. Several mechanisms have been postulated by which the weight reduction can improve the clinical and endocrine characteristics in overweight PCOS patients. Weight loss was found to improve the insulin sensitivity.^{12,15,19} Others reported that weight reduction decreases the cytochrome P450c 17a which is the key enzyme in the synthesis of androgens.²⁰ Furthermore, it has been reported that weight loss increases the sex hormone binding globulin concentrations, indicating an impact on the free testosterone levels or bioavailable hormone.^{15,20} The association between PCOS-related hyperandrogenemia and insulin resistance is well documented.^{1,5,6,9} It has been suggested that the resulting hyperinsulinemia augments the LH-driven production of androgens from the ovarian theca cells in these women.⁵ Several studies of women with PCOS have shown that when insulin secretion is decreased with insulin sensitizing drugs, such as metformin, troglitazone or d-chiro-inositol, the rates of spontaneous ovulation and ovulation in response to clomiphene citrate both increase.^{10,11,22-24} The use of insulin-sensitizing drugs to treat hyperinsulinemia in patients with PCOS is based on the theory that insulin can directly stimulate the ovary to augment ovarian androgen production. The rational basis for its use in the treatment of PCOS, metformin, a biguanide antihyperglycemic drug that used to treat non-insulin dependent diabetes mellitus, reduces hyperinsulinism and ovarian levels of androgens, and it is classified as a category B drug, which means that no teratogenic effect has been demonstrated in vitro.¹⁰ The results of our study showed that women who received metformin treatment over 6-month period had significant improvement in the clinical and endocrine features of PCOS. Furthermore, similar reproductive outcome to women who received metformin for the same duration was observed. These findings are consistent with those reported earlier by others.²²⁻²⁴ Velazquez et al²³ evaluating 22 obese PCOS women for 6 months of metformin treatment found significant decrease in the levels of androgens, LH, fasting insulin and LH:FSH ratio. Resumption of menstrual cyclicity occurred in 96% and pregnancy in 19%. Moreover, Moghetti et al²⁴ studied 21 overweight PCOS women prescribing metformin for 6 months. After treatment, patients had significant improvement in their menstrual cycle frequency and endocrine disturbances. Malkawi and Qublan²² evaluated 16 obese PCOS women with metformin treatment for 6 months, the ovulation rates was 69% versus 25% in the placebo group and pregnancy

rates was 56% versus 16% in the placebo group. In a more recent study, evaluating 19 PCOS patients with morbid obesity, we noticed a significant reduction in the body weight, hormonal parameters, clinical features, and reproductive outcome.¹¹ We suggested that metformin induces weight loss that ameliorates the hyperinsulinemia and hyperandrogenemia, improving the clinical, metabolic, and endocrine disturbances, increasing the ovulation and pregnancy rates. These findings were also observed in the metformin-treated group. However, the mechanism by which metformin reduces the body weight is not clear in our study. Most of our patients who received metformin had a feeling of full stomach and impaired food intake. One of the possible explanations is due to the leptin hypothesis.²⁵ Leptin receptor is located in the hypothalamus and the activation of this central receptor will inhibit the synthesis of the hypothalamic neuropeptide Y (NPY), which is a potent stimulator of food intake. It appears that metformin treatment improves the leptin sensitivity, inhibiting NPY action, impairing food intake that results in body weight reduction. This hypothesis is supported by Fleming et al²⁶ study who found significant reduction in the leptin levels and a significant decrease in BMI in the metformin treated compared with the placebo. On contrast, some studies showed that metformin is not effective for grossly obese PCOS women. Ehrmann et al²⁷ treated 14 overweight PCOS women for 12 weeks found no improvement in BMI, hyperinsulinemia, and androgen excess. This discrepancy might be related to the sample size and the duration of metformin treatment.

In conclusion, it is well known that the reproductive function is adversely affected in women with PCOS and this will be further compromised in the presence of obesity. Amelioration of hyperinsulinemia and hyperandrogenemia with dietary intervention or metformin treatment improves significantly the clinical features and reproductive function in overweight PCOS women. Further studies with larger numbers of patients are needed to confirm these results.

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