COMPARATIVE STUDY BETWEEN THE EFFECTS OF METFORMIN MONOTHERAPY IN OBESE AND NON-OBESE PATIENTS WITH POLYCYSTIC OVARY SYNDROME

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Abstract

Objective: To compare the efficacy of metformin montherapy in improvement of the clinical and biochemical parameters, ovulation and pregnancy rates in obese and non obese patients with polycystic ovary syndrome.

Patients and method: We examined 110 PCOS and 36 controls aged 19-34 years old, body mass index (BMI), A prospective comparative study in Minia University infertility clinic. One hundered infertile women were diagnosed as clomiphene citrate resistant polycystic ovary syndrome at the period starting from November 2009 to August 2010.. The patients were divided into 2 groups .Group (O); included 50 patients with BMI ≥30 kg/m2. Group(N); included 50 patients with BMI ≤30 kg/m2. Both groups received metformin 850 mg tablet twice daily for 12 weeks. The primary outcomes were the ovulation rate, the degree of menstrual regularity , the change of the patients' clinical and biochemical profile after three months of metformin treatment; including the changes in LH/FSH ratio.The secondary outcome was the pregnancy rate.

Results: There was a statistically significant improvement as regards pre- and post-treatment concerning regularity of the cycle ($p<0.0001$) , acne ($p<0.001$) and LH: FSH ratio ($p= 0.015$) and no statistically significant improvement as regard hirustism between both groups .In addition,there was a statistically significant improvement as regards pre- and post-treatment concerning regularity of the cycle ($p=0.0001$ & 0.0002) , acne ($p=0,028$ & 0.033) and LH:FSH ratio($p=0.038$ & 0.495) and no statistically significant decrease as regard hirustism in both groups. However, there were no statistically significant differences between the two groups concerning the ovulation and pregnancy rates after treatment.

Conclusion: Metformin alone may be an effective drug for restoration of menstrual irregularities, LH: FSH ratio, treatment of acne, inducing ovulation and increase pregnancy rates in clomiphene citrate resistant polycystic ovary syndrome. Non obese patients responded better but statistically non significant than obese patients. Further randomized controlled studies on large number of patients are required to compare efficacy of metformin in obese and non obese PCOS patients.

Key Words: Metformin,Polycystic ovary syndrome,Obesity.

Introduction

Polycystic ovary syndrome is a common reproductive and metabolic disorder in which patients will benefit for early recognition and treatment. The prevalence of PCOS varies between 5% and 10% of all women (1). Polycystic ovary syndrome is clinically characterized by chronic anovulation, menstrual irregularities, infertility and obesity in combination with some evidence of androgen excess such as hirsutism, acne and increased serum androgen concentrations (2).

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The current Rotterdam consensus defines PCOS as the presence of at least two out of the three criteria : chronic anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries (PCO), when other disorders of the pituitary, adrenals, or ovary have been excluded (3).

Its clinical manifestations are oligomenorrhea or amenorrhea paired with infertility, hirsutism, obesity, acne and alopecia. Insulin resistance accompanied by compensatory hyperinsulinemia constitutes another major biochemical feature of PCOS. .Obesity and insulin resistance however not a constant features of all PCOS patients; It constitutes an often found criterion in consensus of diagnosis (4).

The fundamental pathophysiologic defect still remains unknown. PCOS appears to be a heterogeneous disorder in which ovarian, and possibly adrenal androgen excess is present along with varying degrees of gonadotropic and metabolic abnormalities (5).

Additionally insulin resistance, hyperinsulinism, type II Diabetes Mellitus, endometrial carcinoma, dyslipidemia and psychosocial dysfunction are presented as other clinical consequences associated with PCOS (6).

Clomiphene citrate (CC) therapy has variable success rates in anovulatory women; however, it is the lowest in women with PCOS, particularly those with insulin resistance. Currently there is increasing evidence that insulin sensitizers are particularly effective in inducing ovulation in patients with PCOS (7).

A magic bullet therapy for PCOS would result in weight loss, improve insulin resistance, restore normal ovulatory cycles, increase fertility, decrease hyperandrogenism, decrease the rate of spontaneous abortions and decrease the risk of GDM. The current front-runner for this magic bullet is the biguanide (metformin) (8).

Metformin, a biguanide, is the most widely used drug for the treatment of type 2 diabetes worldwide. Its primary action is to inhibit hepatic glucose production, but it also increases the sensitivity of peripheral tissues to insulin. The increase in insulin sensitivity, which contributes to the efficacy of metformin in the treatment of diabetes, has also been shown in nondiabetic women with the polycystic ovary syndrome (9).

Nevertheless, the mechanisms underlying the beneficial effects of metformin in the treatment of PCOS remain incompletely understood. Improvement of IR by metformine may not only result from the well-known reduction of hepatic glucose production and increase of peripheral glucose utilization but also from a direct effect on ovarian steroidogenesis, as demonstrated by in vitro studies (10, 11).

Since not all PCOS patients are obese or insulin resistant, it is not clear whether PCOS patients without IR and or obesity also benefit from a therapy with insulin sensitizers.Several smaller studies have suggested positive effects of metformin irrespective of weight and/or presence of IR. For example, Goldenberg et al demonstrated an equal improvement of menstrual irregularities both in insulin-resistant and insulin-sensitive PCOS patients (12).

Many trials were set up to test insulin sensitizers (mainly metformin) for ovulation induction in women with PCOS. These studies have been summarized in several reviews and meta-analyses (13,14,15) however little evidence was produced on the effect of insulin sensitizers (mainly metformin) on the nonobese women without insulin resistance.

The aim of this study was to compare the efficacy of metformin montherapy in improvement of the clinical and biochemical parameters, ovulation and pregnancy rates in obese and non obese patients with polycystic ovary syndrome

Patients and method

The present study was preformed in the infertility clinic in Minia University Hospital. All PCOS patients attending the infertility clinic with diagnosis as CC resistance had been counseled to participate in the study during the period from November 2009 to Augest 2010.

One hundred tweenty patient counseled to participate in the study, only 100 patient had completed the follow up and were equally allocated into two groups: Group (O) (obese patients with BMI $\geq$ 30 kg/m2), and Group (N) (non obese patients with BMI<30 kg/m2). Institutional Review Board (IRB) approval was obtained for the study and informed consent was taken from all included patients.

Inclusion criteria

- Women with subfertilty aged 18 - 40 years of age, diagnosed according to Rotterdam Criteria (3) diagnosis when two of the following criteria were present; oligomenorrhea or amenorrhea , clinical or biochemical signs of hyperandrogenism and PCO (at least one ovary with at least 12 follicles of a diameter of 2–9 mm or a volume >10 ml), and other pituitary, adrenal, or ovarian diseases were excluded .

- Resistance to CC which defined as failure to ovulate after at least 3 consecutive courses of CC in a dosage of 150mg/d from 2nd – 6th day of the cycle.

Exclusion criteria
were patient refusal, presence of other causes of infertility, medical disease affecting patient fertility, drug hypersensitivity, other infertility medications for at least 3 months and patient non compliance for more than 7 days of treatment.

All participant patients were subjected to history talking, general examination ,day 3 vaginal ultrasonography and day 3 hormonal assay (serum FSH, LH, and prolactin). These hormones were assessed by ELISA technique using quomum diagnostic kits. Fasting serum glucose level by one touch method was measuerd.

Both groups received metformin 850 mg tablets twice daily for 12 weeks. Data were collected during the follow up visits with the same physician after 4, 8, 12 weeks respectively. The primary outcomes were; first the ovulation rate, second was the degree of menstrual regularity (28±7).Third was the change of the patients' clinical and biochemical profile before and after inclusion in the study, and after the three months metformin treatment; including the changes in LH/FSH ratio.The secondary outcome was the pregnancy rate.

Timed intercourse was encouraged at the expected time of ovulation. The couples were advised to have sexual intercourse every other day. They were asked to contact the infertility clinic as soon as they have missed period (1 week).

Statistical analysis
SPSS for windows; standard version 10.0.7(SPSS Co., Chicago, IL, USA) was used for the statistical analysis. The results were reported as mean ± SD. The groups were compared by using unpaired t-test and the results obtained before and after metformin therapy were compared by using paired t-test. A P-value < 0.05 was regarded as statistically significant.

RESULTS

One hundred CC resistant PCOS patient were equally allocated into two groups; Group (O) (obese patients with BMI ≥ 30 kg/m2), and Group (N) (non obese patients with BMI<30 kg/m2). Both groups received metformin 850 mg tablets twice daily for 12 weeks.
The demographic parameters of the patients before starting of treatment were shown in table (1). There was a statistically significant improvement as regards pre-and post-treatment concerning regularity of the cycle ($p<0.0001$) , acne ($p<0.001$) and LH: FSH ratio ($p= 0.015$) and no statistically significant improvement as regard hirustism($p = 0.88$) between both groups as shown in table (2).
There was a statistically significant improvement as regards pre- and post-treatment concerning regularity of the cycle (p=0.0001 & 0.0002) , acne (p=0,028 & 0.033) and LH:FSH ratio(p=0.038 & 0.495) and no statistically significant decrease as regard hirustism(p= 0.99 & 0.98) in both groups as shown in tables (3&4).However, there were no statistically significant differences between the two groups concerning the ovulation (p=0.425) and pregnancy rates (p=0.75) after treatment as shown in table (5).

Table (1) :
The demographic parameters of the patients before starting of treatment.

General characteristics	Patients group No = 100
Age in years	
Range (Min-Max):	18-37
Mean ± SD:	24.7±4.3
Duration of infertility in years	
Range (Min-Max):	2-15
Mean ±	3.1±2
Type of infertility	
Primary: No (%)	70 (70%)
Secondary: No (%)	30 (30%)
Weight in Kg	
Range (Min-Max):	58-100
Mean ± SD:	84.5±6.4
Height in Cm	
Range (Min-Max):	152-169
Mean ± SD:	161.3±4.1
Body mass index Kg/m2	
Range (Min-Max):	22-35
Mean ± SD:	31.2±3
Random blood glucose level (mg/dl)	
Range (Min-Max):	74-120
Mean ± SD:	85±14.3

Table (2) :
Comparison between patient groups as regarding the gynecological characteristics before and after treatment.

Gynecological characteristics	Patients group No = 100		P
	Before treatment	After treatment	
Menstrual cycle Regular: No (%) Irregular: No (%)	 37 (37%) 63(63%)	 72 (72%) 28 (28%)	 <0.0001*
Acne Present: No (%) Absent: No (%)	 42 (42%) 58 (58%)	 20 (20%) 80 (80%)	 <0.001*
Hirustism Present: No (%) Absent: No (%)	 30(30%) 70(70%)	 28(28%) 72(72%)	 0.88
LH/FSH ratio 1: No (%) 2: No (%)	 77(77%) 23(23%)	 60 (60%) 40 (40%)	 0.015*

1: LH/FSH ratio >2 **2: LH/FSH ratio <2**

Table (2) shows the difference between pre- and post-treatment. There was a statistically significant improvement as regards pre- and post-treatment concerning regularity of the cycle, acne and LH: FSH ratio and no statistically significant improvement as regard hirustism.

Table (3) :
Comparison between the gynecological characteristics before and after treatment among the nonobese group.

Gynecological characteristics	Nonobese group No = 50		P
	Before treatment	After treatment	
Menstrual cycle Regular: No (%) Irregular: No (%)	 20 (40%) 30(60%)	 38 (76%) 12 (24%)	 0.0001*
Acne Present: No (%) Absent: No (%)	 20 (40%) 30 (60%)	 9(18 %) 41(82%)	 0,028*
Hirustism Present: No (%) Absent: No (%)	 14(28%) 36(72%)	 13(26%) 37(72%)	 0.99
LH/FSH ratio 1: No (%) 2: No (%)	 37(74%) 13(26%)	 26(52%) 24(48%)	 0.038*

1: LH/FSH ratio >2 **2: LH/FSH ratio <2**

Table (3) shows the difference between pre- and post-treatment among nonobese group .There was a statistically significant improvement as regards pre- and post-treatment concerning regularity of the cycle, acne and LH:FSH ratio and no statistically significant decrease as regard hirustism.

Table (4) :
Comparison between the gynecological characteristics before and after treatment among the obese group.

Gynecological characteristics	Obese group No = 50		P
	Before treatment	After treatment	
Menstrual cycle Regular: No (%) Irregular: No (%)	 17 (34%) 33 (66%)	 34 (68%) 16 (32%)	 0.0002*
Acne Present: No (%) Absent: No (%)	 22 (44%) 28 (56%)	 11 (22%) 39 (78%)	 0.033*
Hirustism Present: No (%) Absent: No (%)	 16(32%) 34(68%)	 15(30%) 35(70%)	 0.98
LH/FSH ratio 1: No (%) 2: No (%)	 40(80%) 10(20%)	 30(60%) 20(40%)	 0.495*

1: LH/FSH ratio >2 **2: LH/FSH ratio <2**

Table (4) shows the difference between pre- and post-treatment among obese group. There was a statistically significant improvement as regards pre- and post-treatment concerning regularity of the cycle, acne and LH:FSH ratio and no statistically significant decrease as regard hirustism.

Table (5) :
Comparison between obese and non-obese groups as regarding ovulation and pregnancy rates after treatment.

Ovulation& pregnancy	Obese	Non-obese	P
Ovulation Non-ovulation	20 (40%) 30(60%)	24(48%) 26(52%)	0.425
Pregnancy Non-pregnancy	4(8%) 46(92%)	6(12%) 44(88%)	0.75

Table (5) shows that there were no statistically significant differences between the two groups concerning the ovulation and Pregnancy rates after treatment.

DISCUSSION

Since the role of IR in the pathogenesis of PCOS has been established, many interventional studies have demonstrated a positive effect of insulin-sensitizing agents in the treatment of PCOS. For example, Hahn et al (16) pointed out a positive effect of metformin on hyperandrogenism, chronic anovulation and IR . In accordance with these studies, our results showed that PCOS patients benefit from metformin treatment with regard to hyperandrogenism, menstrual disturbances ,ovulation and pregnancy rate.

In this study, both groups of obese and nonobese PCOS patients clearly showed statistically significant improvements as regarding to acne, menstrual irregularities and LH:FSH ratio and statistically non significant improvements as regarding to hirsutism and improvement in ovulation and pregnancy rates .

Non obese group responded better but statistically non significant than obese group as regarding to acne, menstrual irregularities, LH: FSH ratio, ovulation and pregnancy rates.

In agreement with our study Costello et al., (17) demonstrated the same findings in a double-blind, placebo-controlled study that performed on twenty-three Caucasian women with PCOS, aged between 18–35 yr , with normal glucose tolerance. Women were randomly assigned to double-blind oral metformin or placebo for 6 months. The dose of metformin was increased stepwise, from 500 mg once daily for the first week to 500 mg twice daily for the next week and to 500 mg tid for a further 24 weeks. They concluded that metformin was effective in many women with PCOS, independently of changes in body weight, in attenuating insulin resistance and hyperandrogenemia and in reversing menstrual abnormalities and chronic anovulation.

These findings were in agreement with our study and several previous studies, For example, Nestler et al., (18) demonstrated in a study included one hundred women who received 850 metformin twice daily that insulin-sensitizing drugs increase ovulation rate and ameliorate hyperandrogenemia, even in nonobese women with PCOS.

In addition, Hahn et al., (16) in agreement with our study have demonstrated a positive effect of insulin-sensitizing agents in the treatment of PCOS and pointed out a positive effect of metformin on hyperandrogenism, chronic anovulation, and IR.

Michael (19) demonstrated that hyperandrogenemia was reduced by metformin treatment (500 mg three times daily) for 6 months. In addition, non obese PCOS patients benefited better than obese PCOS. Palomba et al., (20) reported a significant improvement of pregnancy and ovulation rate in comparison with clomiphene and ovarian drilling. Accumulating evidence has shown that the rationale for metformin use makes sense as 2 meta-analyses of randomized controlled trials (RCTs) have shown that the use of metformin alone improves ovulation and pregnancy rates in women with PCOS.

Michael et al., (21) compared metformin cloridrate (850 mg twice daily) plus placebo (group A) versus placebo plus CC (150 mg for 5 d from the third day of a progesterone withdrawal bleeding) (group B).The study included one hundred nonobese anovulatory women with PCOS who received treatment for 6 months. The main outcome measures were ovulation, pregnancy, abortion and live-birth rates. The cumulative pregnancy rate was significantly higher in group A than group B. They concluded that six-month metformin administration was significantly more effective than six-cycle CC treatment in improving fertility in anovulatory nonobese PCOS women.

kumari et al., (22) demonstrated in a study included 17 lean and 17 obese PCOS patients treated with 1500 mg metformin daily that ovulation and pregnancy rates were higher in the lean PCOS group. These studies were in agreement with our study data, showing a positive effect of metformin therapy on endocrine and metabolic variables even in lean and insulin-sensitive women. Also in agreement with our study, a study was done by Michael (19) to determine the clinical, hormonal, and biochemical effects of metformin therapy in obese and nonobese patients with PCOS. Twenty-nine patients with PCOS were treated with 500 mg metformin t.i.d. for 6 months. This study suggested that non obese patients responded better than obese patients to a 1.5 g/day metformin regimen.

In accordance with our study the effect of 6 months of metformin treatment was prospectively assessed by Tan et al., (23) in 188 PCOS patients, divided into three groups according to body mass index (BMI; lean: BMI<25 kg/m2, overweight: BMI 25–29 kg/m2, and obese: BMI30 kg/m2). PCOS patients were evaluated at baseline and following treatment with metformin in a weight-adapted dose for 6 months (body weight <60 kg: 500 mg metformin twice a day (BID), 60–100 kg: 850 mg BID, and 100 kg or BMI30 kg/m2: 1000 mg BID). This study suggested that metformin improves parameters of IR, hyperandrogenemia, anovulation, and acne in PCOS irrespective of pre-treatment IR or obesity.

On the other hand, other studies that assessed metformin effects in hyperandrogenic subjects did not confirm these findings .The reasons for the striking discrepancies among these studies were not readily explained. Interestingly, where insulin levels were reduced by treatment, serum androgens were lowered as well (24).

In this regard, Crave et al., (25) did not observe any additional benefit of metformin over the effects of diet alone as regarding clinical and biochemical feature of PCOS, in a double-blind study comparing the effects of a 4-month low calorie diet vs. diet plus metformin in obese hirsute women. Unfortunately, this study was

not specifically designed to recruit women with PCOS and actually the large majority of patients had regular menses. This weakened any conclusion, as hyperinsulinemia likely plays a major role in the pathogenesis of hyperandrogenism only in PCOS subjects

Furthermore, Tan et al., (23) in a randomized, controlled, double-blinded study recruited 56 women aged 18–45 with PCOS. They were treated with either metformin 850 mg or placebo twice daily for 6 months. The conclusion of this study was, in obese PCOS women, metformin treatment for 6 months lowers body weight, biochemical parameters, while there seems to be little effect on these parameters in non-obese PCOS women.However these findings must be interpreted with caution because of the small number of non-obese patients. It must also be taken into account that obese and non-obese women differed at baseline.

In conclusion, metformin alone is an effective drug for restoration of menstrual irregularities, LH: FSH ratio, treatment of acne, inducing ovulation and increase pregnancy rates in clomiphene citrate -resistant polycystic ovary syndrome. However metformin had a very little effect in treatment of hirsutism in obese and non obese patients with polycystic ovary syndrome. Non obese patients responded better but statistically non significant than obese patients. Further randomized controlled studies on large number of patients are required to compare efficacy of metformin in obese and non obese PCOS patients.

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