

Metformin Treatment for Lean Women with Normal Insulin Levels and Poly Cystic Ovarian Syndrome is Effective: A cohort study

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Abstract

Background: Metformin is insulin sensitizing drug that may improve insulin metabolism in women with poly cystic ovarian syndrome. **Aim:** The aim of this study was to examine the effects of Metformin drug on oligomenorrheic women with polycystic ovary syndrome (PCOS) who had normal body weight as well as normal insulin levels. **Methods:** It was a prospective cohort study undertaken throughout a year (2011) in Al-Sabeen Maternity hospital Sana'a. A total of 31 women with PCOS who met our criteria were studied. Metformin drug (1500 mg / day) was given for each subject for 6 months. Clinical symptoms, menstrual patterns, hirsutism as well as serum levels of luteinizing hormone (LH), Follicular stimulating hormone (FSH), testosterone, estradiol (E2) and 17-OH progesterone were evaluated pre and post treatment. **Results:** Twenty eight women were completed the study, improvement in menstrual cyclicity was observed in 42.9% ($p < 0.001$) and 2/7 women (22.2%) were cured from hirsutism ($P < 0.001$). There were significant decrease in LH concentration, LH/ FSH ratio and an increase in FSH levels ($P > 0.05$). Changes on body mass index (BMI), E2 and progesterone were not significant. **Conclusion:** Metformin administration for lean women with normal insulin levels has a favorable effects on reducing androgen production and restoration of menstrual cycle regularity.

Key words: Poly cystic ovary syndrome; Metformin use; insulin resistant.

Introduction:

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disorder that affects about 6-8% of women during the reproductive age 1. The pathological mechanisms of PCOS are not fully understood but the data indicate that insulin resistance (IR) likely plays a central role in the pathophysiology of PCOS which results in secondary hyperinsulinemia 2. The increased insulin levels leads to excess androgen synthesis by the ovarian theca cells and is made worse by obesity 2. It is reported that IR and thus hyperinsulinemia affects approximately 60-70 % of women with PCOS and 40 – 60% of PCOS women are obese 3. The initial studies have shown that the

agent which ameliorates insulin resistance and reduces circulating insulin levels such as Metformin may improve the condition 4. Several studies reported the beneficial effects of Metformin on the clinical and biochemical parameters of PCOS women 5,6. However, since not all women with PCOS have insulin resistance or obesity, it is unclear if PCOS women with normal body weight and normoinsulinemia also benefit from Metformin treatment. **Aim of the study:** The aim of this study was to explore whether or not metformin therapy can improve the clinical and / or biochemical parameters of PCOS in this sub group of women.

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Subjects and Methods

A descriptive, hospital based study was conducted among women with oligo menorrhea and PCOS who attended outpatient clinic at Al-Sabeen Maternity hospital, Sana'a from Jan 1st to Dec 31, 2011. The study protocol was approved by the institute ethics committee and informed consent was obtained from each participant. The study procedure was in accordance with the guideline of Helsinki declaration. PCOS was diagnosed according to the Rotterdam 2003 criteria 1 in which a women should have at least two of the following criteria: (1) evidence of chronic anovulation or oligomenorrhea (i.e ≤ 8 menstrual periods in the preceding 12 months or menstrual cycles more than 35 days in length); (2) clinical hyperandrogenism (acne or modified ferriman – Gallwey (FG) scores ≥ 8) and or biochemical hyperandrogenism; (3) polycystic ovary (i.e ≥ 12 follicles in each ovary measuring 2-9 mm in diameter); (4) exclusion of other etiologies (e.g: late – onset congenital adrenal hyperplasia (CAH), androgen secreting tumors and Cushing's syndrome). The inclusion criteria were: 1) Women with PCOS as defined above in whom the oligo-menorrhea was the main complaint; 2) BMI between 18.5 – 24.9 kg/m² (Calculated as weight/ (height)² in kg/m²); 3) normal fasting insulin levels (< 12 μ U/L) (measured following overnight fast 10 – 12h during oral glucose tolerance test) 7. None of the subject had significant medical illness, received medications known to affect insulin or glucose metabolism, sex hormones or having contraindication for Metformin drug. A total of 31 subjects met our criteria were initially included in this study. All subjects had detailed history and physical examination. Hirsutism was assessed by two observers using modified FG scoring method. Following an overnight fast during the predictable follicular phase, blood samples were collected between 8.00 and 9.00 am for hormonal assays. These involved luteinizing hormone (LH), follicular stimulating hormone (FSH), total testosterone (TT), free testosterone (FT), estrogen and

progesterone. They measured by chemiluminescence immunoassay (Cobas ® e 411 analyzer, Roche Diagnostic, Hungary). An oral glucose tolerance test (OGTT) was performed following overnight fast. Venous blood samples were taken before ingestion of 75g glucose load and at 30, 60, 90 and 120 minutes after. Also before ingestion of glucose load one additional blood sample was taken to measure the fasting insulin level. Before starting Metformin treatment, all subjects were given general counseling and advised to eat healthy modified diet and to have regular exercise during the course of therapy. Metformin hydrochloride 500mg tablets (Metforal, Menarini International, Italy) was commenced on day 1 of spontaneous or induced menstruation for 6 months. The subjects were instructed to start drug gradually as once daily in the first week, twice daily in the second week, and thrice daily thereafter. Trans vaginal ultrasonography was performed at the day 12 and onwards at weekly interval. The evidence of ovulation was based on the observing a growing follicle that reached size of 18mm or more and subsequently ruptured and confirmed by serum progesterone level (≥ 5 ng/ml) 5-9 days after ruptured follicle. At the end of 6 months, fasting glucose, insulin and all hormonal levels were repeated in the same laboratory using the same kits. Also FG score and BMI were noted. Data for all subjects were computed and analyzed using the SPSS software version 10.1 (SPSS Inc... Chicago. IL., USA). Values were given as mean \pm S.D or percentage as appropriate. The significance between pre-and post-therapy parameters was assessed by Student's- t – test for paired values and Chi-square test and Wilcoxon's sign rank test for non- parametric variables. A P-value <0.05 was considered significant.

Results

Out of 31 patients initially enrolled in the study, three patients were subsequently excluded from the study: two subjects were lost to follow-up and one patient for lack of compliance. Twenty eight patients completed the study. The mean patients age was 26.7 ± 1 and the mean BMI at

recruitment was 23.2 ± 2.2 (range: 19-25) (table 1). After Metformin therapy for 6 cycles there were significant reduction in fasting insulin ($P<0.001$) and fasting glucose levels ($P<0.001$). A statistically significant differences in the means of LH, FSH, LH/ FSH ratio were noted ($P<0.05$). Also the total testosterone (TT) and free testosterone (FT) concentrations showed significant reduction after Metformin treatment ($P<0.001$). There were no significant changes noted in the estradiol and progesterone levels after medication. Metformin treatment induced normal menstrual cycles was noted in twelve patients (42.9%) ($P<0.001$) and two patients (2/9) were completely cured from hirsutism and the severity of the remaining 7 cases was only modestly reduced after therapy. Metformin drug was well tolerated by all subjects. None of the subjects suspended the drug because of side effects, despite some experienced transient bloating, diarrhea and nausea during the first few weeks of treatment. Table 2 summarizes the effects of Metformin on hormone concentrations and clinical parameters.

Table 1: Characteristic of the women with PCOS (N=28)

Variables	Mean \pm S.D or n (%)
Age (year)	26.7 ± 1.3
Body mass index (BMI) (kg/m ²)	23.2 ± 2.2
Marital status	
• Married	19 (67.8)
• Single	11 (39.2)
Parity	
• Para1	9 (47.3)
• Para 2	2 (10.5)
• None	8 (42.1)
Educational level	
• Primary School	13 (46.4)
• Secondary School	8 (28.6)
• University	3 (10.4)
• Illiterate	4 (14.2)

Table 2: The effects of Metformin treatment (1500 mg/day) for 6 cycles on hormone concentrations and clinical parameters (N= 28).

Variable	Baseline	After treatment	P- value
BMI (kg/ m ²)	23.3 ± 2.2	22.3 ± 2.1	NS
LH (mu/ml)	14.11 ± 1.2	12.6 ± 1.7	$P<0.001$
FSH (miu/ml)	3.2 ± 0.28	4.18 ± 0.32	$P<0.001$
LH/ FSH ratio	4.4 ± 0.53	3.0 ± 0.91	$P<0.001$
Testosterone (ng/ml)	91.6 ± 4.7	79.94 ± 3.9	$P<0.001$
Free testosterone (ng/ml)	0.934 ± 0.06	0.737 ± 0.047	$P<0.001$
Estradiol (pg/ ml)	71 ± 6.8	72.8 ± 4.7	NS
Progesterone (ng/ml)	1.32 ± 0.7	1.58 ± 0.92	NS
Fasting insulin mu/L	6.65 ± 1.9	4.9 ± 1.1	$P<0.05$
Fasting glucose mg/dl	86.7 ± 3.6	79 ± 2.7	$P<0.001$
FG score ≥ 8	9 (32.1)	7 (25)	NS
Menstrual regularity	None	12 (42.9)	$P<0.001$

The values are expressed as mean \pm S.D or n (%), BMI: body mass index, FG: Ferriman – Gallwey

Discussion

Our study showed that hyperinsulinemia was not associated with PCOS in our subgroup of women. It is reported that insulin resistance (IR) affects approximately two thirds of women with PCOS³, this implies that at least one third of PCOS women have no IR as is the case in the present study. It is likely therefore that several unknown factors are involved in the fundamental pathogenesis of PCOS and no one in isolation can be considered responsible for this syndrome. Our result demonstrated that Metformin administration for 6 cycles was associated with improving ovulatory function and cyclic regularity in 42.9% of our population. Kashyap and colleagues (2004) in a systematic review found that Metformin induced ovulation in 47% of patients and the drug was 50% better than placebo for ovulation induction in infertile PCOS patients⁸. Similar results are reported by other studies

9,10. Some studies observed higher rate of ovulation with Metformin alone or in combination with low dose (100-150mg) clomiphene citrate 11. In the present study which included only those with normal weight and normoinsulinemic PCOS women, it is expected that the effect of Metformin is minimal.

Theoretically Metformin acts to reduce insulin levels and increases insulin sensitivity 12, therefore the androgen synthesis by the ovaries is reduced². It is found that this mechanism of Metformin action is commonly associated with spontaneous restoration of menstrual cycling and ovulation in PCOS women with insulin resistance¹³. However, in women with normal insulin levels, it appears that the causes of oligo/anovulation are complex and not fully understood^{10,14}. It is unlikely that ovulation dysfunction in these women can be explained solely by IR and the presence of an intrinsic abnormality of folliculogenesis is a possibility worthy further study. Accordingly, we believe that the improvement of ovulation noted in this study can be explained by the direct effect of the drug on androgen production by the ovarian thecal cells as recently demonstrated¹⁵.

Our result showed that the mean BMI was decreased by nearly 3.9% after Metformin therapy. The previous studies have reported conflict results.

Tan et al (2007) found that the Metformin use is associated with significant decrease of the body weight and BMI in the overweight and obese groups 16. In another study, it was observed to decrease body weight even in non-obese women with PCOS¹⁷. Conversely, other investigators found that Metformin has no effect on BMI or waist circumference¹⁸. However, it is suggested that the effect of Metformin on the body weight is minimal and dose- dependent which is in line with our results³.

The present study has certain limitations. The small sample size may not allow our results to be generalizable but it serves as a preliminary data for further research. Also we did not test other androgenic hormones such as dihydroepiandrosterone (DHEA) and androstenedione

because it is generally accepted that testosterone is the measurement of choice for the investigation of female hyperandrogenism⁵.

Conclusion

The present study demonstrates that Metformin use (1500 mg/ day) 6 months for oligomenorrheic, normal BMI and normoinsulinemic PCOS women has a favorable effects on resumption of regular menstrual cyclicity, and improving hirsutism score.

There were significant decrease in the LH levels, LH/FSH ratio and an increase in the FSH concentration levels. It is likely therefore that Metformin may act directly to improve significantly the ovarian function.

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