

## Rosiglitazone , Metformin or both for Treatment of Polycystic Ovary Syndrome

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### Abstract

This study was designed to show the advantages of using the combination of metformin and rosiglitazone over using each drug alone in treatment of women with polycystic ovary syndrome (PCOS). Forty four women with PCOS were classified into 3 groups , group 1 received rosiglitazone (4mg/day) for 3 months , group II received metformin ( 1500 mg/day) for three months and group III received the combination ( rosiglitazone 4mg/day + metformin 1500 mg/day) for the same period of treatment . The blood samples were drawn before treatment and after 3 months of treatment . The fasting serum glucose , insulin , progesterone , testosterone , leutinizing hormone were measured before and after treatment. The reduction of serum insulin , glucose , homostasis model assessment of insuline resistance ( HOMA-IR ) , LH and testosterone levels were greater in the group received the combination of rosiglitazone with metformin than that those taken each one alone. Testosterone levels decreased significantly (  $P < 0.05$  ) from baseline level  $1 \pm 0.04 \text{ ng/ml}$  to  $0.073 \pm 0.32 \text{ ng/ml}$  after treatment with combination. The rate of ovulation is 29.4%, 36.4% , 62.5% in rosiglitazone , metformin and combination of both , respectively. The combination of rosiglitazone with metformin has more beneficial effect on ovulation rate.

**Key words:** polycystic ovary syndrome, rosiglitazone, metformin, ovulation rate .

### الخلاصة

هذه الدراسة صممت لعرض الفوائد من استعمال خليط من الميتفورمين والروزيكليتازون على استعمال كل دواء منفردا عند علاج النساء المصابات بمتلازمة المبيض متعدد الاكياس . اربع واربعون امرأة مصابة بمتلازمة المبيض متعدد الاكياس قسمن الى ثلاث مجموعات : المجموعة الاولى تناولت الروزيكليتازون بجرعة 4ملغ يوميا لمدة ثلاثة اشهر و المجموعة الثانية تناولت الميتفورمين بجرعة 1500 ملغ يوميا لمدة ثلاثة اشهر اما المجموعة الثالثة فقد تناولت خليط من الروزيكليتازون بجرعة 4ملغ يوميا والميتفورمين بجرعة 1500 ملغ يوميا لنفس مدة العلاج . نماذج الدم سحبت قبل العلاج وبعد ثلاثة اشهر من العلاج . ان التغيير في مستويات الكلوكوز ، الانسولين ، البروجيسترون ، الهورمون اللوتيني والتستوستيرون كان ملحوظا اكثر في خليط الروزيكليتازون و الميتفورمين مما في حالة اخذ كل دواء منفردا . كما ان مستوى التستوستيرون يقل معنويا عن مستوى الشروع بعد العلاج بالمركب . وكانت نسبة القابلية على انتاج البيض هي 29,4 36,4 62,5 في الروزيكليتازون والميتفورمين وكلتاها معا على الترتيب ان خليط الروزيكليتازون و الميتفورمين له تأثير نافع على نسبة انتاج البيض .

### Introduction

Polycystic ovary syndrome (PCOS) is the most common abnormality in women during reproductive age, it is a heterogeneous disorder of uncertain etiology<sup>(1)</sup>. It is characterized by chronic anovulation and hyperandrogenism<sup>(2)</sup> affecting approximately 5-10 % of reproductive age women. The association between hyperinsulinemic insulin resistance and PCOS is well recognized and may play an important pathogenic role in development of PCOS<sup>(3)</sup>. Obese and lean women with PCOS manifest insulin resistance independent on body weight, although obesity is an additive factor which aggravates insulin resistance<sup>(4)</sup>. There is some data to suggest that insulin enhances the effect of LH on preovulatory ovarian follicle arrest<sup>(5)</sup>. It is possible that hyperinsulinemia due to insulin resistance drives the LH affect on ovarian theca cells to

cause androgen excess which are intrinsically programmed to produce more androgens<sup>(6)</sup>. Excess androgens are known to interfere with the process of follicular maturation , thus inhibiting ovulation and producing more arrested follicles. It has been postulated that in PCOS ovaries there is an increased resistance to all insulin functions , except for steroidogenic effect and the ultimate result is excess androgen production even with normal insulin level<sup>(7)</sup>. Metformin is a biguanide hypoglycemic agent that is approved for the management of type II diabetes<sup>(8)</sup>. Its main mechanism of action is the reduction of hepatic glucose production ( inhibition of gluconeogenesis ). It also increases insulin mediated glucose utilization in peripheral tissue and decreases intestinal absorption of glucose<sup>(9)</sup>.

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Several authors <sup>(10,11)</sup> have demonstrated the additional benefits of using metformin such as these related to menstrual cycle regulation and induction of ovulation, protection from pregnancy losses ,improvement of cardiovascular risk factors ,moreover metformin markedly increases both spontanous ovulation rate and clomiphene-induced ovulation rate for obese women with PCOS <sup>(12)</sup> . Many studies have shown improvements in ovulatory function , development of normal menses , and restoring of fertility <sup>(13)</sup>. In spite all of these benefits , many workers reported that metformin effect may be to some extent transient and some cellular adaptation may occur during more prolonged therapy <sup>(14)</sup> . Rosiglitazone was approved in (1999) by food and drug administration (FDA) as an oral antidiabetic agent for the management of type II diabetes as monotherapy and in combination with oral hypoglycemic agents <sup>(15)</sup> . Rosiglitazone increases insulin sensitivity without stimulating insulin secretion, its mode of action is by binding and activation of the nuclear peroxisome proliferators activator gamma (PPAR- $\gamma$ ) which is found in key target tissues for insulin action as adipose tissue, skeletal muscle and liver. Activation of (PPAR- $\gamma$ ) regulates the transcription of insulin-responsive genes involved in control of glucose and fatty acid metabolism <sup>(9,11)</sup> . Therefore this study was designed to show whether combination of ( rosiglitazone and metformin ) has advantages over using each drug alone in the treatment of women with PCOS.

## Methods and Materials

This study was conducted at Baghdad city in AL-Elwia maternity teaching hospital from October-2004 till June-2005. The study groups included 60 Iraqi women, (44) case with PCOS aged 17-40 years with a mean of age 27.3 $\pm$ 5.07 years , and 16 normal control subjects aged 18-38 years with a mean of age 27.1 $\pm$ 6 years. The patients included in this study were diagnosed with PCOS were non-diabetic, non-hypertensive and non-pregnant. The patients were under gynecologist supervision during period of treatment. The diagnosis of PCOS was made by gynecologist depending on ultrasound examination, clinical features and laboratory tests (hormonal assay). The patients involved in this study were on normal diet. They were divided randomly into 3 groups:

1. Group 1 included 17 patients (BMI 28.8 $\pm$ 3.9 Kg/m<sup>2</sup>), age 29.7 $\pm$ 6.4 years. The

patients received rosiglitazone 4mg daily in two divided doses (2mg) in the morning and (2mg) in the evening after meals for 3 months.

2. -Group II included (11) patients (BMI 29.1 $\pm$ 5.2Kg/m<sup>2</sup>), age 24.9 $\pm$  years). The patients received metformin 1500mg daily in three divided doses (500mg after each meal ) for three months.
3. -Group III included (16) patients (BMI 34.2 $\pm$ 6 Kg/m<sup>2</sup> ) , age 26.5 $\pm$ 4 years. The patients received a combination of the two drugs ( rosiglitazone 4mg/day + metformin 1500mg/day ) for three months.
4. -Control group included (16) normal women (BMI 30 $\pm$ 4.8 Kg/m<sup>2</sup>), age 27.1 $\pm$ 6 years.

### Sample collection:

Eight milliliters (8ml) of venous blood samples used in this study were drawn from PCOS patients. The first sample was collected before treatment as a baseline level, and after three months of treatment with insulin sensitizing agents. Fasting blood samples were used for the measurement of glucose , insulin, hormones (LH, testosterone and progesterone). Blood samples were left at room temperature for 30 minutes for clotting, centrifugated and then serum was separated and collected in small aliquots(0.5ml) and stored at (-20 C) until biochemical and hormonal analysis was performed. The serum was used for measurement of fasting blood sugar, insulin ,testosterone, LH and progesterone levels.

### Biochemical and hormonal assay:

Fasting insulin levels were determined using a commercial kit obtained from Randox, using Radioimmunoassay (RIA) method <sup>(17,18)</sup> . Serum testosterone levels were determined using a commercial kit obtained from Immunotech, based also on (RIA) <sup>(19)</sup> . By using of a kit from Immunotech, the radioimmunoassay of progesterone is competition assay <sup>(20)</sup> . Serum LH determined using kit from Immunotech, by the immunoradiometric assay (IRMA) which is sandwich type assay <sup>(21)</sup> . Fasting serum glucose was measured by a commercial kit obtained from BIODIAG, using the enzymatic method <sup>(22)</sup> .

**Diagnosis of infertility** depends on that inability of any couple to conceive a child within a 12 months period of unprotected coitus ( sexual intercourse) <sup>(23)</sup> .

**Body mass index (BMI)** was calculated using the standard formula :

BMI=weight (kg)/height (m)<sup>2</sup>. Obese patients were defined as having BMI > 27 Kg/m<sup>2</sup> <sup>(24,25)</sup> .

**Homeostasis model assessment of insulin resistance (HOMA\_IR)** was calculated using the following formula:

$HOMA-IR = \frac{\text{basal glucose (mmol/L)} \cdot \text{basal insulin}(\mu\text{IU/ml})}{22.5}$

Insulin resistance patients were defined as having  $HOMA > 2.7$  (26).

The drugs used in this study were: Rosiglitazone 4mg tablets purchased from (Sunpharma)- India- and metformin 500mg tablets purchased from (MB and C) -syria-

### Statistical analysis

- 1-The results were expressed as  $\text{mean} \pm \text{SD}$  mean.
- 2- Student T-test was used to examine the difference in the mean of parameters tested.
- 3- P-value of less than (0.05) was considered significant.

### Results

The most patients in this study were with oligomenorrhea (68.1%) and (22.7%) of the patients were infertile. The hirsutism was obvious symptom in (63.6%) of the patients

( table 1). The combination of metformin and rosiglitazone reduced the levels of serum insulin, glucose , HOMA-IR, LH and testosterone which are more than that produced by rosiglitazone or metformin alone (tables 2 , 3 and 4 )(P<0.05).The testosterone was significantly decreased (P<0.05) only after treatment with combination compared to the baseline levels. The ovulation rates were 29.4%, 36.4%, 62.5% in rosiglitazone, metformin and combination of both , respectively (table 5).

**Table(1): demographic data of 44 patients with PCOS.**

Character	Number of patients (%)
Obese	31(70.4%)
Lean	13(29.5%)
Amenorrhea	10(22.7%)
Oligomenorrhea	30(68.1%)
Regular cycle	4(9%)
Infertility	10(22.7%)
Hirsutism	28(63.6%)

**Table (2): Effect of treatment of rosiglitazone(4mg/day) on levels of insulin, glucose, HOMA-IR,LH and testosterone in group1.**

Variables	Control levels (n=16)	Baseline levels (before treatment) (n=17)	After treatment (n=17)(%)
<b>Insulin (<math>\mu\text{U/ml}</math>)</b>	8.4 $\pm$ 1.7	15.6 $\pm$ 5.5a	10.4 $\pm$ 3.6(33.5)
<b>Glucose (mg/100ml)</b>	82 $\pm$ 4.9	89.8 $\pm$ 7	84 $\pm$ 5.8(6.4)
<b>HOMA-IR</b>	1.7 $\pm$ 0.43	3.4 $\pm$ 1.4a	2.1 $\pm$ 0.9(38.2)
<b>LH (m<math>\mu</math>/ml)</b>	4.5 $\pm$ 0.15	11.6 $\pm$ 3.4a	10.6 $\pm$ 3.1a(8.6)
<b>Testosterone(ng/ml)</b>	0.34 $\pm$ 0.01	0.94 $\pm$ 0.44a	0.71 $\pm$ 0.43a(24.4)

Values are means $\pm$ SD

n= No. of women.

%= percentage of change compared with base line levels.

a p<0.05 for comparison with control group.

HOMA= homeostasis model assessment of insulin resistance.

LH= Leutinizing hormone.

**Table (3) : Effect of treatment with metformin(1500mg/day) on levels of insulin , glucose , HOMA-IR,LH and testosterone in group II.**

Variables	Control levels (n=16)	Baseline levels (before treatment) (n=11)	After treatment (n=11)(%)
<b>Insulin (<math>\mu</math>U/ml)</b>	8.4 $\pm$ 1.7	14.5 $\pm$ 4.3a	10.3 $\pm$ 2.8(28.9)
<b>Glucose (mg/100ml)</b>	82 $\pm$ 4.9	84.2 $\pm$ 4.2	82 $\pm$ 5.1(2.6)
<b>HOMA-IR</b>	1.7 $\pm$ 0.43	2.9 $\pm$ 0.9a	2 $\pm$ 0.5b(13)
<b>LH (m<math>\mu</math>/ml)</b>	4.50.15 $\pm$	12.4 $\pm$ 4.7a	11.5 $\pm$ 3.9a(7.2)
<b>Testosterone(ng/ml)</b>	0.34 $\pm$ 0.01	0.91 $\pm$ 0.51a	0.71 $\pm$ 0.37a(21.9)

Values are means  $\pm$ SD.

N=No. of women.

%=percentage of change compared with baseline level.

a P<0.05 for comparison with control group.

**Table (4): Effect of treatment with the combination of metformin(1500 mg /d) and rosiglitazone (4mg/d) on the levels of insulin , glucose , HOMA-IR,LH and testosterone in group II.**

Variables	Control levels (n=16)	Baseline levels (before treatment) (n=16)	After treatment (n=16)(%)
<b>Insulin (<math>\mu</math>U/ml)</b>	8.4 $\pm$ 1.7	21.2 $\pm$ 8a	12.5 $\pm$ 4.8(41)
<b>Glucose (mg/100ml)</b>	82 $\pm$ 4.9	90.3 $\pm$ 8.3a	84.1 $\pm$ 6.5(6.8)
<b>HOMA-IR</b>	1.7 $\pm$ 0.43	5 $\pm$ 1.5a	2.6 $\pm$ 0.8(48)
<b>LH (m<math>\mu</math>/ml)</b>	4.50.15 $\pm$	11.9 $\pm$ 2.8a	10.2 $\pm$ 2.3a(14.2)
<b>Testosterone (ng/ml)</b>	0.34 $\pm$ 0.01	1 $\pm$ 0.46a	0.73 $\pm$ 0.32a,b(27)

Values are means  $\pm$ SD.

n= no. of women .

%=percentage of change compared with baseline level.

a P<0.05 for comparison with control group.

b P<0.05 for comparison with base line alone .

**Table (5): Ovulation rate in PCOS patients for treatment with insulin sensitizing agents.**

Groups Secondary outcome	Group I (n=17)	Group II (n=11)	Group III (n=16)	Total
<b>Ovulation</b>	5(29.4)	4(36.4%)	10(62.5)%111	19
<b>No ovulation</b>	12(70.6%)	7(63.6%)	6(37.5%)	25
<b>Total</b>	17	11	16	44

n=no. of women

Group 1: women treated with rosiglitazone 4mg/d alone.

Group 2: women treated with metformin 1500mg/d alone.

Group III : women treated with combination of rosiglitazone 4mg/d and metformin 1500mg/d.

## Discussion

In this study, the administration of insulin sensitizing agents rosiglitazone and metformin alone or in combination for three months showed non-significant reduction ( $P > 0.05$ ) in serum glucose levels, serum insulin levels nor HOMA-IR index. The efficacy and percentage of improvement was seen to be more obvious in combination group than with either drug alone (table 2,3 and 4). Rosiglitazone showed more improvement than metformin. However, in present study, rosiglitazone and metformin treatment improved insulin resistance because there was an improvement in fasting insulin and fasting glucose levels, similar results were reported by other studies<sup>(27,28)</sup>. All groups of patients who received rosiglitazone and metformin alone or in combination showed a slight (non-significant) decline in LH levels when compared with baseline levels. Lack of change in LH levels also reported by many researchers<sup>(28,29)</sup>. The effect of rosiglitazone and metformin combination for three months was associated with significant decline in testosterone levels ( $p < 0.05$ ) (table 4). The study also shows a greater decrease in insulin and HOMA-IR index leading to more decrease in testosterone level. These results are in agreement with studies showed a reduction in serum androgen levels after the reduction of insulin levels by insulin sensitizing agents, and these effect were independent in body weight<sup>(28,30,29)</sup>. In general, the favorable effect of insulin sensitizing agents on hyperandrogenemia in PCOS may be due to reduced pituitary secretion of LH, reduced ovarian androgen secretion, and increased levels of sex hormone binding globulin (SHBG)<sup>(31)</sup>. The administration of rosiglitazone or metformin alone or both of them for three months demonstrated an improvement in ovulation rate assessed by measurement of mid-luteal phase progesterone level in group III more than group II and I (table 5). This may be due to the synergistic effect of two drugs which lead to decrease the testosterone significantly ( $P < 0.05$ ). The percentage of ovulation was (62.5%, (36.4%) and (29.4%) in groups III, II, I respectively. Several studies investigated effect of metformin on menstrual cyclicity, and a significant improvement in the frequency of menstrual cycles has been reported, with an increase in the percentage of ovulatory cycles as assessed by mid-luteal phase progesterone<sup>(32,27)</sup>. K.J Meenanakumaari et al (2004) found a significant negative correlation between insulin and progesterone, and between progesterone and

LH concentration in PCOS women treated with metformin and suggested that insulin resistance / hyperinsulinemia may be responsible for low progesterone levels during the luteal phase in PCOS. The luteal progesterone may be enhanced in PCOS by decreasing insulin levels with metformin<sup>(33)</sup>. Richardo Azziz et al (2001) studied the effect of rosiglitazone on menstrual cyclicity and ovulation in PCOS women. Azziz reported an increase in the mean rate of ovulation in dose-related fashion and he expected an improvement in the menstrual cycle after the improvement in ovulation<sup>(34)</sup>. Nicholas A. Cataldo et al (2006) showed a favorable effect of rosiglitazone on menstrual pattern or ovulation independent of rosiglitazone dose, furthermore they have found that ovulation occur in association with only modest change in insulin resistance and insulinemia and claimed either that a small metabolic improvement is sufficient to promote preovulatory follicular maturation or that rosiglitazone exerts its effect independently of insulin<sup>(35)</sup>. Similar results were reported by Didem Dereli et al (2005)<sup>(36)</sup>. In conclusion it is preferable to use a combination of rosiglitazone and metformin in infertile PCOS women as it has more potent effect in the improvement of ovulation rate. The combination is also more beneficial to alleviate the hyperandrogenemia in women with PCOS.

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