

## Predictors of Rosiglitazone Success in Ovulation Induction among Women with Polycystic Ovary Syndrome Resistant to Clomiphene Citrate

Wasan Wajdi MBChB, FICOG, FACOG

### Abstract:

**Background:** In women suffering from polycystic ovary syndrome, correction of hyperinsulinemia results enhances spontaneous ovulation or alternatively, the responsiveness to ovulation induction agents such as clomiphene citrate.

**Objective:** To study the effect of rosiglitazone on ovulation induction in obese, clomiphene citrate resistant women with polycystic ovarian syndrome.

**Design:** Double –blind, randomized, placebo-controlled trial.

**Setting:** Women with Polycystic ovarian syndrome attending as outpatients in Baghdad teaching hospital.

**Patient and methods:** During the period from October 2010 to the end of December 2011, forty infertile women were diagnosed as having PCOS according to the Rotterdam criteria; all patients had previously received clomiphene citrate and were diagnosed as having resistance to this drug. Those patients were randomized into two treatment groups. Subjects in group 1 (n=15) was randomized to receive rosiglitazone 4 mg/ day with a placebo on cycle days 5-9. Group 2 (n=25) was randomized to receive rosiglitazone 4 mg /day with clomiphene citrate on cycle days 5-9. The duration of the study was 3-6 months. The primary outcome was ovulation as defined by serum progesterone greater than 5 ng/dl at mid luteal phase of cycle. Secondary outcomes were pregnancy and changes in insulin sensitivity and androgens.

**Results:** Overall, 24 of 40 (60%) women, who were previously resistant to clomiphene citrate, successfully ovulated. In subjects taking rosiglitazone alone (Group 1), 6 of 15 (40%) subjects ovulated compared with 18 of 25 (72%) women randomized to rosiglitazone with clomiphene citrate (Group2), three subjects in Group 1 became pregnant, resulting in uncomplicated live births and 12 subjects in Group 2 conceived, with nine successful live births and three first trimester, spontaneous abortion.

**Conclusions:** Short –term rosiglitazone therapy enhances both spontaneous and clomiphene- induced ovulation in obese women with polycystic ovarian syndrome. Rosiglitazone therapy improves insulin sensitivity and decreases hyperandrogenaemia primarily through increases in Sex hormone binding globulin.

**Keyword:** Rosiglitazone, polycystic ovary syndrome, clomiphene citrate.

### Introduction:-

An ovulation is responsible for about 20% of female infertility of which polycystic syndrome is a major cause<sup>(1,2)</sup>.

Women with PCOS demonstrate peripheral resistance to insulin which generally presents with hyperinsulinemia a compensatory increase in plasma insulin levels<sup>(2,3)</sup>. The degree of hyperinsulinemia is more profound in obese patients, although the presence of insulin resistance appears to be independent of weight<sup>(4,5)</sup>. Hyperinsulinemia contributes significantly to the ovarian hyperandrogenism and chronic anovulation commonly observed with PCOS<sup>(6, 7, 8)</sup>.

PCOS patients with hyperinsulinemia also appear to be at greater risk for developing dyslipidemia, type 2 diabetes mellitus, hypertension and coronary heart disease<sup>(9, 10, 11)</sup>.

Currently, the accepted treatment for women with PCOS associated infertility is ovulation induction using clomiphene citrate, however, a significant proportion of PCOS patients are resistant to the usual doses of clomiphene citrate. Often, the only alternative is to proceed with ovulation induction using exogenous gonadotropin, which carry the risk of high order multiple pregnancy and ovarian hyper stimulation, as well as excessive financial cost<sup>(12,13)</sup>. Therefore, attention has turned to the correction of hyperinsulinemia as a method of ovulation induction, particularly in obese women who demonstrate the greatest degree of insulin resistance.

Rosiglitazone maleate, which is indicated as monotherapy in the treatment of type 2 diabetes, directly increases peripheral insulin sensitivity without stimulating insulin secretion. It given in a dose 4mg/day, its adverse events is retention of fluid which include peripheral edema and dilutional decrease in hematocrit (if it given for long duration), but it is not associated with the gastrointestinal side effects commonly reported with metformin and which often limits patient compliance. In this study, we observed the effect of rosiglitazone on induction of ovulation in obese women who were resistant to standard doses of clomiphene citrate.<sup>(13)</sup>

### Patient and method:-

This prospective study was carried out in outpatient clinic of Baghdad teaching hospital and in Private clinic from October 2010 to the end of the December 2011. Forty women were included in this study between 18-37 years old. All of them complain from infertility due to polycystic ovarian syndrome which was diagnosed by ultra sonography and hormonal analysis (LH, FSH, LH/FSH ratio) and according to the definition of PCOS by national institutes of health conference on PCOS1990.

Eighteen of them presented with primary infertility and 22 presented with secondary infertility who had previously received Clomiphene Citrate for 3-6 months.

All the forty women had a body mass index (BMI) of greater than 26 Kg/m (BMI was calculated by using weight (Kg)/ height (m<sup>2</sup>), failed to ovulate

when use clomiphene citrate at a dosage of 150 mg/day, and expressed a desire for pregnancy.

Exclusion criteria included a history of diabetes or hepatic or hematological disease and the use of any medication for at least 3 months before enrollment in this study, Cushing syndrome, thyroid dysfunction, and hyperprolactinemia were excluded. Patients were evaluated at baseline and 3 -6 months of treatment with rosiglitazone 4mg daily. Patients were questioned about tolerance and drug related adverse effect.

Venous blood samples were taken after overnight fasting between 8:00-10:00am, and the measurements of (LH, serum total and free testosterone, SHBG, fasting glucose, fasting insulin, fasting insulin/fasting glucose ratio, HbA1c) at baseline and 3-6 months of treatment with rosiglitazone .

The women in both groups were given a 5 day course of medroxy progesterone acetate 10 mg/day-induced withdrawal bleeding and started rosiglitazone 4 mg/ day in the first day of the cycle. The women were then randomized into either Group 1 or Group 2 by an allocation sequence generated from a random number table and assigned through consecutively numbered, sealed envelopes.

Group 1, fifteen women start to take their rosiglitazone 4 mg/ day in the first day of the cycle and, starting on day 5 of the cycle, took a placebo tab daily for 5 days. Group 2, twenty five women continued their rosiglitazone 4 mg/ day and, starting on day 5, took clomiphene citrate 50 mg/ day, for 5 days. Ultrasound for each woman in both group was done at mid cycle (Day 11 Or 12) for measurement

of dominant follicle. Single blood sample was taken from each woman at midluteal phase (day 21-24) of cycle for serum progesterone level as an indicator of corpus luteum function. Serum progesterone level more than 5 ng/ml was considered as ovulatory level.

For those women without evidence of ovulation, rosiglitazone was continued and subjects were given another medroxyprogesterone acetate – withdrawal menses to initiate treatment cycle 2. Starting on day 5 of their next cycle, Group 1 subjects took a placebo tab daily for 5 days, while Group 2 subjects took clomiphene citrate 100 mg/ day.

If no ovulations occur, continued rosiglitazone and repeated cycles for 3-6 months.

The primary outcome was ovulation, as defined by mid luteal Serum progesterone level more than 5ng/ml in either treatment cycle. Secondary outcome included pregnancy as well as changes fasting serum glucose, insulin, glycosylated hemoglobin (HbA1c), total testosterone, sex hormone binding globulin (SHBG), BMI with rosiglitazone therapy.

**Result:-**

This study includes forty patients, treatment compliance was good, and none of patient reported drug related adverse event. No abnormalities were observed in complete blood count or in renal function test after 3-6 months of rosiglitazone:

1. Patient characteristics before (baseline) and after 3-6 months Of the rosiglitazone therapy shows that there was no change in the waist/hip ratio and in BMI (table 1).

**Table (1): Mean SD of BMI and waist to hip ratio in patients with PCOS before and after rosiglitazone treatment.**

Parameters	Before rosiglitazone	After rosiglitazone	P value
BMI(Kg/m2)	40.4± 2.4	41.1±2.7	NS
W/H	0.86±0.08	0.85±0.06	NS

2. Changes In insulin and glucose parameters with rosiglitazone treatment:- there were no significant change in either fasting glucose or HbA1c values after treatment with

rosiglitazone .However, fasting insulin level declined after treatment (P=0.003 paired t-test). This resulted in the normalization of mean glucose to insulin ratio (table2).

**Table (2): Changes in insulin and glucose parameters after treatment with rosiglitazone**

Parameters	Before rosiglitazone	after	P value
Fasting glucose	88.2±1307	84.9±11.9	> 0.5
Fasting insulin	28.9± 13.3	17.7±7.1	<0.003
Glucose/insulin ratio	3.8±2.0	5.5±2.2	<0.003
HbA1C (%)	5.5±0.6	5.6±0.6	>0.5

3. Changes in androgen parameters before and after 3-6 months of the rosiglitazone therapy shows that there were significant decreases in the total and free testosterone. Whereas SHBG

levels increased after treatment. However no significant change in LH level. There was also a significant decrease in level of DHEA-S (Table3).

**Table (3):** Hormone results before and after rosiglitazone therapy

Parameters	Before	After rosiglitazone	P value
Total Testosterone(ng/dl)	96.3± 17.3	56.1± 5.8	P=0.01
Free Testosterone(pg/ml)	5.8± 0.6	3.4± 0.5	P=0.001
SHBG (nmol/L)	18.3± 3.4	25.8± 6.6	P=0.009
DHEA-S(ng/ml)	1508.7± 181.9	1081.3± 180.8	P= 0.04
LH(miu/ml)	10.1± 0.82	9.1± 0.84	Ns

4. Twenty four of forty patients (60%) studied who were previously resistant to clomiphene citrate, reverted regular ovulatory cycles within 3-6 months of treatment (table 4). In patients taking rosiglitazone alone (Group 1), six of

fifteen (40%) patients ovulated compared with 18 of 25 (72%) women who were randomized to rosiglitazone with clomiphene citrate (Group 2).

**Table (4):** ovulation results by treatment group.

	Group1	Group2	Total
Ovulation	6 (40%)	18 (72%)	24
No ovulation	9 (60%)	7 (28%)	16
Total	15	25	40

Note: Group1 vs. Group 2 ovulation rate: p= .04

**Discussion:-**

Clomiphene citrate (CC) resistance, persistence of an ovulation after a standard dose, and discrepancy between ovulation and pregnancy rates with CC therapy paved the way for another oral therapy that overcomes the previous gaps.

Ehrmann et al. performed the first trial with rosiglitazone in a group of PCOS women who had failed to respond to CC, the ovulation rate was 87.5%<sup>(14,15)</sup> thereafter, many reports released confirming the efficacy of insulin sensitization therapy. The mode of action of it is by binding to the transcription factor peroxisome proliferators activated receptor-γ (PPAR-γ) which promote synthesis of glucose transporters and up regulate expression of multiple genes<sup>(16)</sup>.

In this study, we observed an improvement in insulin resistance, as measured by fasting glucose to insulin ratio.

The improvement was entirely obtained by reduction in fasting insulin level. Consistent with the mechanism of rosiglitazone therapy we did not observe a significant reduction in fasting glucose. Thiazolidinediones enhance peripheral insulin sensitivity and overall glucose disposal. Which result in greater reduction in postprandial glucose excursions, as compared to fasting level<sup>(17)</sup>. In addition, treatment with thiazolidinediones is not associated with occurrence of hypoglycemia. Therefore a significant reduction in fasting glucose would not expect in non diabetic subject.

The improvement of insulin sensitivity resulted in a reduction in ovarian androgen production because levels of both total and free testosterone

were significantly reduced. Level of SHBG increased with therapy, further reducing the bioavailability of circulating androgen.

Interestingly, LH level did not change with therapy of rosiglitazone, this finding agreement with previous studies with troglitazone which show reduction in circulating androgen level without any change in LH level<sup>(16,17)</sup>.

Previous studies on the effect of rosiglitazone in women with PCOS are done. Azziz et al<sup>(18)</sup> compared women with PCOS who received either rosiglitazone and clomiphene citrate or clomiphene citrate only and observed that combined therapy with rosiglitazone and clomiphene citrate resulted in a significant decrease in insulin and serum-free testosterone. The ovulation in this study is about 72%. Ehrmann et al.<sup>(14,15)</sup> treated obese clomiphene-resistant women with PCOS either with rosiglitazone and placebo or rosiglitazone and clomiphene citrate. The ovulation happened in 87.5% of women taking rosiglitazone and clomiphene citrate; and 23.5% of women taking rosiglitazone only.

Dunaif et al treated clomiphene-resistant women with rosiglitazone and clomiphene citrate, they reported ovulation 92 %

<sup>(19)</sup>.in this study the ovulation rate 60%, this difference may be explained by the small sample size.

In summary, short-term rosiglitazone therapy enhances ovulation among women with PCOS resistant to clomiphene citrate by improvement of insulin sensitivity and decreases hyperandrogenaemia primarily through increases in SHBG.

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- \* Dept of Obstetrics & Gynecology Mustansiriyah College of Medicine.