Effect of Rosiglitazone on Insulin Resistance, Ovulation and Pregnancy in Women with Polycystic Ovarian Syndrome

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Abstract:

Summary

Objective: To evaluate the effects of rosiglitazone on insulin resistance, reproductive disturbance in women with polycystic ovarian syndrome (PCOS).

Design: prospective study.

Setting: women with PCOS attending as out patients of private clinic and Baghdad teaching hospital.

Patient & Methods: this study included thirty obese PCOS women with an age ranging from (18-37) years old. The body mass index and waist/ hip ratio of patients were calculated before and after 3-6 months of rosiglitazone therapy. Venous blood sample for fasting glucose, fasting insulin, fasting insulin/ fasting glucose ratio, HbA1C, LH, SHBG, DHEA-S, total and free testosterone were evaluated before and after 3-6 months of 4mg daily treatment with rosiglitazone. In addition, Transvaginal ultrasound was done at mid cycle to demonstrate dominate follicle. Midluteal progesterone was also measured to detect ovulation.

Result: A significant decrease was observed in serum fasting insulin, fasting glucose/ insulin ratio, DHEA-S, total and free testosterone and waist / hip ratio after 3-6months of rosiglitazone therapy.

-BMI (body mass index) remained unchanged.

-Six of thirty patients studied reverted regular ovulatory cycle after 3months of treatment while other sixteen patients reverted ovulation after 6 months of treatment.

Conclusion: rosiglitazone is a promising insulin sensitizer increase ovulatory frequency and ameliorate hyperandrogemia in obese women with PCOS.

Key wards: polycystic ovary syndrome insulin resistance rosiglitazone, ovulation, pregnancy.

Introduction

Polycystic ovarian syndrome is the most common endocrine-gynecological disorder of women in the reproductive age. It affects 5-10% of women characterized by hyperandrogenism, menstrual disturbance (oligomenorrhea or amenorrhea and chronic anovulation. [1,2] Approximately 44% of women with PCOS are obese and 60% display insulin resistance [2,3]. Hyperinsulinemia contributes to the hyperandrogenism by increasing ovarian androgen production and by suppressing hepatic production of SHBG with consequent increase in free testosterone level [4].

The hyperinsulinemia found in PCOS is more profound in obese patients, although the presence of insulin resistance appears to be independent of body weight [5]. Presence of Acanthosis Nigricans in women with PCOS indicate sever insulin resistance and high risk for type 2 diabetes [6,7].Women with hyperandrogenism, insulin resistance and insulin receptors mutation have been observed in those women [8,9].

The diagnosis of PCOS include the presence of two out of three which include:[10]

1-Oligo-and/or anovulation.

2-Clinical and/or biochemical signs of hyperandrogenism (hirsutism, acne, androgen alopecia. the elevation of free testosterone and/or testosterone, are the biochemical indicator).

3-Polycystic ovaries on u/s scan include the presence of 12 or more follicles in each ovary measuring 2-9mm in diameter, and increased ovarian volume more than 10ml.

Hyperinsulinemia appear to be associated with excessive androgen production from both the ovary and adrenal gland, although the mechanism is unclear.

Ovarian hyperandrogenism lead to arrest follicular development and subsequent anovulation. Insulin also inhibits hepatic production of SHBG, thus worsening the hyperandrogenic picture [11].

In the past, therapeutic approaches to PCOS have focused on suppressing ovarian androgen production or ovulation induction. Recently, insulin sensitizers have been used to reduce the level of hyperinsulinemia and its negative impact on ovarian function and possibly to prevent long term consequence of hyperinsulinemia .Women with PCOS are at higher risk of hypertension dyslipidemia, type two diabetes and cardiovascular disease .[11,12]

Rosiglitazone is a member of thiazolidinediones

(TZD) family that has been shown to be effective in treatment of type two diabetes. TZDs are newer oral antidiabetic agent that exerts their insulin-sensitizing action through the peroxisome proliferator -activated receptors that found in a number of tissues include the liver, skeletal muscle and adipose tissue. [13]

Rosiglitazone increase the uptake and utility of glucose in the periphery and decrease hepatic gluconeogensis. [13]

Patient & Method

This prospective study was carried out in private clinic and Baghdad teaching hospital. Thirty women with an age ranging from 18-37years old were included in this study, all of the women had polycystic ovarian syndrome by ultrasonography and hormonal analysis and according to the definition of PCOS by national institutes of health conference on PCOS1990.[10]

The 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's syndrome, thyroid dysfunction, and hyperprolactinaemia 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.

The body mass index (BMI) using the standard formula (weight (kg)/height (m2) and the waist/hip ratio were calculated. Obese patient were defined as having BMI more than 26.8kg/m2 .a waist/hip ratio less than 0.8 was considered normal.[10] 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, DHEAS were taken before and after 3-6months of rosiglitazone therapy ,in addition transvaginal u/s for each patient at mid cycle (D10orD11)for measurement of dominant follicle. Single blood sample was taken from each patient at midlutial phase (D21-D24) of cycle for serum progesterone level as an indicator of corpus luteum function. Serum progesterone level more than 5ng/ml was considered as ovulatory level.

Result

This study includes thirty patient, 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 and after rosiglitazone therapy shows that there was a significant decrease in the waist/hip ratio with no change in BMI (**table 1).**

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).**

3-Changes in androgen parameters before and after rosiglitazone therapy shows that there were significant decrease in the total and free testosterone .Where as SHBG levels increased after treatment .However no significant change in LH level. There was also a significant decrease in level of DHEA-S (**Table3).**

4-Six of thirty patients (20%) studied reverted regular ovulatory cycles after 3 months of treatment, while 16 of remaining twenty four patients reverted ovulation after 6 months of treatment, two patients became pregnant. Ovulation was confirmed using mid luteal serum progesterone level that was more than 5ng/ml after the onset of spontaneous menstruation. Length of cycle during treatment varied from 28-32 day.

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

Parameters	Before Rosiglitazone (Baseline)	Post rosiglitazone	P value
BMI (kg/m^2)	40.4± 2.4	41.1±2.7	NS
W/H	0.86±0.08	0.81±0.06	P<0.001

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

Parameters	Baseline	After rosiglitazone	P value
Fasting glucose	88.2±13.7	84.9±11.9	>0.5
Fasting insulin	28.9±13.3	17.7±7.1	<.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

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

Discussion

In this study, there were no changes in the BMI. Dunaif et al [14] did not report changes in the BMI using troglitazone. As expected, leptin had a positive correlation with the BMI pre, and post treatment with rosiglitazone. It is known that leptin is significantly correlated with fat mass, but insulin has also been reported to have an effect on leptin synthesis. Chronic, but not acute, hyperinsulinemia has been reported to increase the leptin mRNA expression in adipocyte and serum leptin level. [15]

Despite the absence of changes in BMI, the waist/hip ratio in our patient decrease significantly after 3-6 months of treatment, suggesting that there was a fat redistribution with increase caloric storage in subcutaneous adipocyte, which would not be associated with increased cardiovascular risk. Ehrmann et al.[16] found no change in BMI with decreased waist/hip ratio (redistribution or regional adipocyte by using a dual energy X-ray absorptiometry scan when they treated their PCOS subject with troglitazone.

Rosiglitazone therapy 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. These changes are most likely caused by improvement of insulin sensitivity, which resulted in ameliorate of hyperinsulinemia and reduction of ovarian androgen production.

Interestingly, LH level did not change with therapy this finding agreement with previous studies with troglitazone which show reduction in circulating androgen level without any change in LH level. [17]

Rosiglitazone therapy also resulted in significant decrease in circulating level of adrenal androgen DHEA-S. Azziz et al.[17] observed similar effect on DHEA-S level with troglitazone administration for 20 weeks . It is not clear whether the decrease in DHEA-S level is a result of decrease in insulin level or is due to the direct effect of rosiglitazone on the steroidogenic enzyme in the adrenal gland. In recent study, Rosiglitazone treatment for 6 months in women with POS reduced the adrenal androgen response to corticotrophin. [18]

In this study, there was an improvement in insulin resistance, as measured by the 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 [19,20].Furthermore, my subject were not diabetic and this trial was likely too short in duration to reliably demonstrate a reduction in HbA1c. 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.

In summary, the result indicate that rosiglitazone improve insulin sensitivity and glucose tolerance in obese women with PCOS and severe insulin resistance. It also helps to restore ovulation and attenuate ovarian androgen production without weight gain or other side effect. Use of rosiglitazone appear to be an effective method in the management of obese PCOS women with severe insulin resistance

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