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Original Article

Rosiglitazone: Effect on spontaneous and clomiphene citrate induced ovulation in Polycystic Ovary Syndrome

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Abstract

Objectives : To observe the effect of rosiglitazone on spontaneous and clomiphene citrate induced ovulation in patients of polycystic ovary syndrome (PCOS). *Methods:* Thirty diagnosed patients of PCOS were divided into two groups. Group I received only rosiglitazone and patients in Group II were given both rosiglitazone and clomiphene citrate for a period of three months. Serum levels of leutinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, prolactin, progesterone, fasting glucose, and lipids were estimated before and after treatment and compared using paired student 't' test. Ovulation and pregnancy rates were noted. *Results :* Ovulation rates of 40% (6/15) and 66.67% (10/15) and pregnancy rates of 26.67% (4/15) and 40% (6/15) were recorded in group I and II respectively. No significant effect on other parameters was observed except a decrease in LH levels after treatment ($P<0.01$). *Conclusion :* Rosiglitazone appears to be a promising adjunct in management of insulin resistance and anovulation associated with PCOS.

Key words : Polycystic Ovary Syndrome, rosiglitazone, clomiphene citrate, anovulation insulin resistance.

Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disorder, affecting approximately 5% of women and is a common cause of infertility, menstrual irregularity and hirsutism [1]. Recently, an international consensus expanded the definition of PCOS to include women who demonstrate two of the following three characteristics: 1) chronic anovulation; 2) chronic hyperandrogenism; 3) polycystic ovaries on ultrasound [2].

Basic etiology of PCOS includes somatotrophic axis dysfunction and is caused by hyperinsulinemic insulin resistance due to point mutation of insulin receptor gene [2]. Traditionally, medical induction of ovulation using clomiphene citrate has been the first line of treatment. It is an estrogen analogue and a functional hypothalamo-pituitary-ovarian axis is required for its action [3]. It has been documented that although clomiphene citrate leads to ovulation induction in 90% of cases the number of pregnancies achieved is much lower than expected [4]. It has also been observed that treatment with insulin sensitizers can lead to more regular ovulation. Rosiglitazone is a thiazolidinedione, a new class of drugs which improve

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insulin resistance in patients with type-II diabetes mellitus and has also been tried for treatment of PCOS. It is a potent and highly selective agonist for the nuclear peroxisome proliferator activated receptor gamma (PPAR-γ). PPAR-γ increases transcription of certain insulin-sensitive genes, thereby improving insulin sensitivity. It also helps in resumption of ovulation in premenopausal anovulatory women with insulin resistance [5].

This study was undertaken to evaluate the effects of rosiglitazone alone and in combination with clomiphene citrate on ovulation and conception and changes in serum levels of leutinizing hormone (LH), follicular stimulating hormone (FSH), testosterone prolactin, progesterone fasting blood glucose and lipids in patients of PCOS.

Methods

This study was conducted on 30 patients of PCOS, desiring pregnancy after getting their informed consent and obtaining approval by local ethical committee. Any local, uterine or adnexal cause for infertility was ruled out by performing speculum, bimanual vaginal examination, hystero-salpingography and studying husband's semen. Husband semen analysis was also done to rule out any defect in spermatozoa. These patients were then divided into two groups. In group I, patients received rosiglitazone 4mg B.D. starting from day one of menstrual cycle for three months continuously. In group II, patients received rosiglitazone 4mg B.D. starting from day one of menstrual cycle and clomiphene citrate 50 mg O.D. starting from day one for five days for a maximum of three months.

A fasting blood sample was collected by venipuncture and serum was estimated for sugar and lipid profile using enzymatic methods [6-10] and for leutinizing hormone (hLH) and follicle stimulating hormone (hFSH) using immunoradiometric assay on third day of first menstrual cycle [11]. Serum progesterone and testosterone were estimated by radioimmunoassay [12] and serum prolactin (hPRL) by immunoradiometric assay on day 24 of menstrual cycle [11]. All the investigations were repeated on 24th day of third menstrual cycle to analyze the effect of treatment. Primary outcome was considered to be ovulation (serum progesterone > 5ng/mL) and secondary outcome included pregnancy as well as effect on other parameters. All the patients were subjected to premenstrual endometrial biopsy to rule out tubercular endometritis.

Data for all patients before and after treatment was statistically analyzed using paired student 't' test.

Results

All the patients were between 20-40 years of age group, married and were willing to be pregnant. Out of them, 16 had presented with primary infertility and 14 had secondary infertility. No significant improvement in weight, body mass index (BMI) and hirsutism was observed after treatment with rosiglitazone. Mean weights of patients before and after treatment were 62.0±7.30 and 61.69±7.05 Kg respectively ($p>0.05$). Mean BMI was 25.93±3.22 before treatment and 25.70±3.20 Kg/m^2 after the treatment. The mean hirsutism score (Ferriman Gallwey score) before and after therapy were 9.96±6.20 and 9.5±5.56 respectively ($p>0.05$).

Seven patients had normal cycles and no change was observed after treatment with rosiglitazone. Out of 18 patients, who presented with oligomenorrhea, 11 resumed normal cycles and out of four patients, who presented with secondary amenorrhea, three patients developed oligomenorrhea and one developed normal

Table 1. Effect of rosiglitazone on day 24 serum progesterone(n=30).

	Serum progesterone	**First cycle n=15**	**Second cycle n=15**	**Third cycle (n=15)**
Group I	<5ng/mL (no ovulation)	15	13	11
	>5ng/mL (ovulation)	0	2	4
Group II	<5ng/mL (no ovulation)	14	12	9
	>5ng/mL (ovulation)	1	3	6

Table 2. Effect of rosiglitazone on serum levels of various hormones and laboratory parameters.

Parameter	Before treatment Mean ± S.D. (range)	After treatment Mean ± S.D. (range)	p value
LH (mIU/mL)	12.1±10.18 (5.4-60.4)	8.93±3.17 (4.8-18.0)	<0.01
FSH (mIU/mL)	2.76±0.81 (1.0-4.8)	2.84±0.87 (1.0-4.8)	>0.05
Testosterone (ng/dL)	109.81±24.04 (69-169)	108.63±22.98 (72-164)	>0.05
Prolactin (ng/mL)	13.43±2.63 (8.9-18.0)	13.19±2.59 (8.0-18.0)	>0.05
Fasting Glucose (mg/dL)	83.87±7.94 (70-102)	83.0±8.39 (70-96)	>0.05
Total cholesterol (mg/dL)	170.1±20.62 (133-227)	169±19.91 (128-225)	>0.05
HDL cholesterol (mg/dL)	43±6.83 (30-56)	44.13±6.42 (32-58)	>0.05
LDL cholesterol (mg/dL)	104.87±19.33 (74-159)	103.57±18.10 (80-154)	>0.05
Triglycerides (mg/dL)	126.47±46.26 (58-228)	126.03±44.25 (60-220)	>0.05

Table 3. Rates of ovulation and conception.

	Group I (n=15)		Group II (n=15)	
	Ovulation rate	Conception rate	Ovulation rate	Conception rate
First cycle	0%	0%	6.67%	0%
Second cycle	13.33%	9.1%	20%	13.33%
Third cycle	26.67%	20%	40%	30.77%
Total	40%	27.27%	66.67%	40%

cycles. One patient had presented with polymenorrhea and resumed normal cycles after three months treatment with rosiglitazone. Effect of rosiglitazone treatment on day 24 serum progesterone is show in table 1 and on different hormone concentrations and laboratory parameters is shown in table II. Ovulation and conception rates in two groups are shown in table III.

Three pregnancies occurred in group I. One patient delivered by LSCS at 38 weeks due to fetal distress. Second patient had threatened abortion at nine weeks but delivered vaginally at 37 weeks. Third patient had spontaneous abortion at six weeks. In group II, six pregnancies occurred, out of which one patient delivered twins at 36 weeks. One patient had spontaneous abortion at eight weeks. Rest four patients delivered vaginally at full term.

No major side effects were noticed during the

treatment period. One patient experienced headache and two patients reported early morning swelling of fingers which disappeared after few hours. Rest of the patients tolerated the drug well.

Discussion

There was no significant effect seen on BMI and hirsutism of the patients after treatment with rosiglitazone. Improvement in menstrual cycles was observed as is also reported by other authors [13]. No significant change in levels of fasting glucose and lipid profile was observed after treatment with rosiglitazone. Ghazeeri et al and Belli et al have also reported similar results [13,14].

In the present study, there was significant decrease in serum LH and LH/FSH ratio as is reported by other authors [13-15]. No significant decrease was noted in levels of serum testosterone and FSH levels as also reported by Ghazeeri et al [14]. But in another study, these levels decreased significantly after treatment with rosiglitazone for a period of three months[15]. It may be due to raised levels of sex hormone binding globulin (SHBG) as have been reported by some authors [13,14].

Ovulation rate in group I was found to be 40% , in group II was 66.67% with total rate being 53.33% which are comparable to other studies [14]. Conception rate for group I was seen to be 27.27%, for group II being 40% and overall rate was 34.6% which is more than reported by Ghazeeri et al [14]. These differences may be due to longer duration of treatment in the present study i.e. three months as compared to two months in the reported study.

Conclusion

Thus rosiglitazone appears to be a well tolerated and a promising adjunct treatment to clomiphene citrate in the management of PCOS associated insulin resistance and anovulation.

References

1. Yao MWM, Schust DJ. Infertility. In: Rebecca DR, Paula AH, Eli YA, eds. Novak's Gynecology. 13th edn. Philadelphia: Lippincott Williams & Wilkins, 2002; pg974-1001.
2. Hershlag A, Peterson CM. Endocrine disorders. In: Rebecca DR, Paula AH, Eli YA, eds. Novak's Gynecology. 13th edn. Philadelphia: Lippincott Williams and Wilkins, 2002; pg876-9.
3. Mitwally MF, Casper RF. Aromatase inhibition for ovarian stimulation: future avenues for infertility management. Curr Opin Obstet Gynecol 2002;14:255-63.
4. Gysler M, March CM, Mishell DR, et al. A decade's experience with an individualized clomiphene citrate regimen including its effect on the postcoital test. Fertil Steril. 1982;37:161-7.
5. Werner AL, Travaglini MT. A review of rosiglitazone in type 2 diabetes mellitus. Pharmacotherapy 2001;21:1082-99.
6. Trinder P. Determination of blood glucose using an oxidase-peroxidase system with a non-carcinogenic chromogen. J Clin Pathol. 1969;22:158-61.
7. Giovanni B, Harold D. Quantitative determination of sequm triglycerides by use of enzymes. Clin Chem. 1973;19:476-82.
8. Lopes-Virella MF, Stone P, Ellis S, et al. Cholesterol determination in high density lipoproteins separated by three different methods. Clin Chem. 1977;23:882-4.
9. Allain CC, Poon LS, Chan CSG et al. Enzymatic determination of total serum cholesterol. Clin Chem. 1974;20:470-5.
10. Rifai N, Bachorik PS, Albers JJ. Lipids, lipoproteins and apolipoproteins. In: Burtis CA, Ashwood ER, eds. Tietz Textbook of Clinical Chemistry. 3rd edn. Philadelphia: W.B. Saunders, 1999;pg843-4.
11. Woodhead JS, Addison GM, Hales CN. Radioimmunoassay and saturation analysis. The immunoradiometric assay and related techniques. Br Med Bullet. 1974;30:44-9.
12. Abraham GE, Manlimos FS, Garza R. Radioimmunoassay of steroids. In: Abraham GE ed. Handbook of Radioimmunoassay. New York: Marcel Dekker, 1977;pg597-620.
13. Belli SH, Graffigna MN, Oneto A, et al. Effect of rosiglitazone on insulin resistance, growth factors and reproductive disturbances in women with polycystic ovary syndrome. Fertil Steril. 2004;81:624-9.
14. Ghazeeri G, Kutteh WH, Bryer-Ash M, et al. Effect of rosiglitazone on spontaneous and clomiphene citrate induced ovulation in women with polycystic ovary syndrome. Fertil Steril 2003;79:562-6.
15. Shobokshi A, Shaarawy M. Correction of insulin resistance and hyperandrogenism in polycystic ovarian syndrome by combined rosiglitazone and clomiphene citrate therapy. J Soc Gynecol Investig 2003;10:99-104.