ORIGINAL ARTICLE

Comparison of Efficacy of Metformin Versus Pioglitazone in patients with Polycystic Ovarian Syndrome

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ABSTRACT

Aim: To compare the efficacy ofpioglitazone and metforminin women with polycystic ovary syndrome.
Methods: This randomized trial was conducted at Department of Obstetrics & Gynecology, THQ Hospital Jampur from February 2016 to August 2016. Total 70 patients with polycystic ovary syndrome having 20-40 years of age with duration of disease >3 month were recruited.
Results: The mean age of women in group A was 29.97±5.28 years and in group B was 30.37±5.63 years. Mean duration of marriage in study group A was 4.74±2.40 years and in study group B was 4.91±2.25 years. The mean duration of disease in study group A was 3.69±1.59 years and in study group B was 3.94±1.84 years. Efficacy of Group A (metformin group) was 19 (54.29%) while in Group B (pioglitazone group) was 29 (82.86%) with p-value = 0.010.
Conclusion: This studyconcluded that Pioglitazone is more effective as compare to metformin for ovulation induction in women with polycystic ovary syndrome.
Keywords: Polycystic, ovaries, ovulation, metformin, pioglitazone.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a commondisorder endocrine in females of childbearing age. Reported prevalence of PCOS is from 6.8% to 18%[1,2]. Cases of PCOS present with obesity, infertility and hyperandrogenism[3]. In cases of PCOS, excessive secretion of androgen results in increased estrogen precursors in granulosa cells. In these cases, in presence of hyperinsulinemia, luteinizing hormone receptorsappears earlier in granulosa cells, which results the start ofaromatase (estrogen synthetase) in these cells. This phenomenon results in increasedestrogen production, with the positive feedback on luteinizing hormone and the negative feedback on follicle-stimulating hormone, and finallyinterruption of folliculogenesis[4]. Insulin resistance and hyperandrogenism causes the chronic anovulation and infertility[5].

Multiple treatment plans have been suggested for the treatment of infertility in cases of PCOS, including decrease in weight,metformin,thiazolidinedione, clomiphene citrate, letrozole, and assisted reproductive technology[6].

Metformin restores the menstrual cycles and improve the fertility in initiallyoligo-ovulatory and anovulatory cases of PCOS. Several studies reported the effects of metformin on endometrium, so as to create suitable environment for pregnancy[7]. Metformin use is associated withimproved ovulation, improvement in menstrual cycle and a decrease in circulating levels of androgen[8].

In year 1998, thiazolidinediones(TZDs) were introduced as a new class of insulin sensitizers, suggested the responses as similar to the use of metformin[9]. TZDs, including pioglitazone, are peroxisome proliferator-activated receptor (PPAR)-c agonists that induce adipogenesis and have insulin-sensitizing and anti-diabetic properties[10].

The rationale of this study was to compare the efficacy of metformin and pioglitazone in restoring ovulation induction in patients with PCOS in local population. Although previously their efficacy had been studied but that was very little work done on this. So our study would not only provide the local stats on this but also provide clinicians with a more efficacious drug for ovulation induction in PCOS patients which ultimately restores their fertility. Then on the basis of the clinical evidence, some practical recommendations could be made in our routine guidelines for recommending the better drug in these particular patients for ovulation induction.

MATERIAL AND METHODS

This randomized trial was conducted at Department of Obstetrics & Gynecology, THQ Hospital Jampur from February 2016 to August 2016. After approval from ethical review committee and after taking written informed consent form every patient, total 70 patients with polycystic ovary syndrome having 20-40 years of

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age with duration of disease >3 month were recruited.

Pregnant and nursing women, patients with chronic disease i.e. chronic liver disease, chronic renal failure, history of ischemic heart disease, patients with hypothyroidism (presence of all these; TSH >5.2 mIU/L and FT_3<1.5 pg/ml, FT_4<0.8 pg/ml, T_3<70ng/dl, T_4<5.2 µg/dl), patients with hyperprolactinemia i.e., prolactin levels >500 mIU/L, patients with any drug intake-like Anti-diabetic (or) Oestrogen and progesterone were excluded from the study.

Patients were randomly divided into two groups i.e. Group A & B. In group A patients, Metformin (Glucophage, Merck) with dose of 1500 mg per day in three divided doses were given for three months. In group B patients, Pioglitazone (Poze, AGP) 15mg (BID) was administered for three months. At the end of 3 months, all the patients were evaluated for efficacy (Yes/No).

Efficacy was deemed as yes if there was ovulation induction (presence of all these; biphasic basal temperature curve, a follicle with a diameter ≥16 mm on transvaginal ultrasonography and progesterone ≥14 nmol/l in the second half of a menstrual cycle), otherwise considered as no. All the collected data along with demographic profile was entered in pre-designed proforma.

All the data was entered and analyzed by using SPSS version 18. Age, duration of disease, duration of marriage and BMI were presented by mean ± SD. Qualitative variables like diabetes mellitus and efficacy of both groups were presented by frequency and percentage. Comparison between the groups with respect to efficacy was analyzed by chi square test. P value ≤0.05 was considered as statistically significant. Effect modifiers were controlled by stratification of data in terms of age, duration of disease, duration of marriage, diabetes mellitus (yes/no) and BMI (<30kg/m^2 or >30kg/m^2). Post-stratification chi square test was applied to see the effect of these on efficacy and p-value ≤0.05 was taken as significant.

RESULTS

Age range in this study was from 20 to 40 years with mean age of 30.17±5.42 years. The mean age of women in group A was 29.97±5.28 years and in group B was 30.37 ± 5.63 years. Mean duration since marriage was 4.83± 2.32 years. The mean duration since marriage in group A was 4.74±2.40 years and in group B was 4.91±2.25 years. Mean duration of disease was 3.81±1.70 years. The mean duration of disease in group A was 3.69±1.59 years and in group B was 3.94±1.84 years. Mean BMI was 29.89±3.25 kg/m^2. The mean BMI in group A was 29.94±3.31 kg/m 2 and in group B was 29.83 ± 3.23 kg/m^2.

Comparison of efficacy between the both groups was done. Out of 35 patients of group A (metformin group), efficacy of the treatment was noted in 19(54.29%) patients while in group B (pioglitazone group) efficacy of the treatment was 29(82.86%). Significantly (P = 0.010) higher efficacy rate was noted in Group B as compare to Group A (Table 1).

Patients were divided into two age groups, age group 20-30 years and age group 31-40 years and comparison of efficacy between the treatment group A & B for age was done. In age group 20-30 years, total 19 (54.29%) patients belonged to treatment group A and 18(51.43%) belonged to treatment group B. Efficacy of the treatment was noted in 11 (57.89%) patients of treatment group A and 15(83.33%) patients of treatment group B and the difference was insignificant with p value 0.091. In age group 31-40 years, 16(45.71%) patients belonged to treatment Group A and 17 (48.57%) belonged to treatment group B. efficacy of the treatment was noted as 08 (50.0%) and 14 (82.35%) in treatment group A and B respectively. The difference between the efficacy of both treatment was statistically significant (P = 0.049) (Table 2).

Total 23 (65.71%) and 24 (68.57%) patients of treatment group A and B was found with ≤ 5 years of marriage. The efficacy of the treatment group A and B was 12(52.17%) and 18 (75%) respectively. The difference of efficacy between the both treatment groups was statistically insignificant (P=0.104). Total 12 (34.29%) and (31.43%) patients of treatment group A and B was found with >5 years of marriage. The efficacy of the treatment group A and B was 7(58.33%) and 11 (100.0%) respectively. The difference of efficacy between the both treatment groups was statistically significant (P = 0.016) (Table 3).

Distribution of patients according to duration of disease was done. Total 21(60%) of group A and 20(57.14%) patients of group B was belonged to ≤ 3 years of duration of disease. Treatment was found effective in 9(42.86%) patients of group A and 16 (80.0%) patients of group B. The difference of efficacy between the bot treatment groups was statistically significant (P=0.015). Total 14(40%) of group A and 15(42.86%) patients of group B was belonged to >3 years of duration of disease. Treatment was found effective in 10(71.43%) patients of group A and 13 (86.67%)patients of group B. The difference of efficacy between the bot treatment groups was statistically insignificant (P = 0.311). Table 4

Total 20(57.14%) and 21(60%) patients of treatment group A and B were non-obese and

efficacy of treatment was noted in 11(55%) and 19 (90.48%) patients and the difference was significant (P = 0.010). Total 15 (42.86%) and 14(40%) patients of treatment group A and B were obese and efficacy of treatment was noted in 8(53.33%) and 10(71.43%) patients and the difference was insignificant (P = 0.316) (Table 5).

Table 1: Comparison of efficacy between the both groups

Study group	Efficacy		Total
	Yes	No	
A	19(54.29%)	16(45.71%)	35
B	29(82.86%)	6(17.14%)	35

P = 0.010

Table 2: Age distribution of the patients

Study group	Efficacy		Total
	Yes	No	
20-30 years (P = 0.091)			
A	11(57.89%)	08(42.11%)	19(54.29%)
B	15(83.33%)	03(16.67%)	18(51.43%)
31-40 years (P = 0.049)			
A	08 (50%)	08 (50%)	16(45.71%)
B	14(82.35%)	03(17.65%)	17(48.57%)

Table 3: Distribution of patients according to duration since marriage

Study group	Efficacy		Total
	Yes	No	
≤ 5 years (P = 0.104)			
A	12(52.17%)	11(47.83%)	23(65.71%)
B	18(75%)	06(25%)	24(68.57%)
>5 years (P = 0.016)			
A	07(58.33%)	05(41.67%)	12(34.29%)
B	11(100%)	0	11(31.43%)

Table 4: Distribution of patients according to duration of disease

Study group	Efficacy		Total
	Yes	No	
≤ 3 years (P = 0.015)			
A	09(42.86%)	12(57.14%)	21(60%)
B	16(80%)	04(20%)	20(57.14%)
≤ 3 years (P = 0.015)			
A	09(42.86%)	12(57.14%)	21(60%)
B	16(80%)	04(20%)	20(57.14%)

Table 5: Distribution of patients according to BMI

Study group	Efficacy		Total
	Yes	No	
Non-obese (P = 0.010)			
A	11(55%)	09(45%)	20(57.14%)
B	19(90.48%)	02(9.52%)	21(60%)
A	08(53.33%)	07(46.67%)	15(42.86%)
B	10(71.43%)	04(28.57%)	14(40%)

DISCUSSION

The purpose of this RCT was to compare the efficacy ofpioglitazone and metforminin women with PCOS. In our study, efficacy ofmetformin group was 54.29% while in pioglitazone group was 82.86%.

In one study, in cases of PCOS, metformin alone shown a significant benefit oninducing ovulation.[11]Sangeeta S has documented the restoration of ovulation in 44.2% patients of PCOS treated with metformin.[12] In one study women with PCOS were treated with pioglitazone, improvement was noted in hirsutism,menstrual frequency,and insulin sensitivity.[13]Ota H et al[14] has reported ovulation induction in 77.78% caseswith PCOS while treated with pioglitazone.In a meta-analysis by Li XJ et al[15] it was found that TZDs were more effectiveas compare to metformin in decreasing the levels of free testosterone and dehydroepiandrosterone sulfate (DHEA) (P=0.002) after 3 months of treatment.In one meta-analysis it was noted that the use of metformin in PCOS efficiently induced ovulation.[16] TZDs have also improved insulin sensitivity and reduces the androgenaemia in cases of PCOS.[17]Brettenthaler et al[18] reported tha ttreatment with pioglitazone, ovulation induction ratewas increased from 5.6% to 41.2% as compared to placebo group. Glueck et al[19]documented that pioglitazone in combination with metformin in non-responsive PCOS cases, improved the insulin sensitivity, reduced the levels of androgenand induced ovulation. Hirotaka et al[14] reported that 7/9 (77.7%) patients succeeded in pregnancy in 11.1 weeks after start of pioglitazone, 4/7 (57%) of those pregnant women conceived in 1st cycle.

CONCLUSION

This study concludes that Pioglitazone is more effective than metformin for ovulation induction in women with PCOS. So, we recommend that Pioglitazone should be used as a first line therapy for ovulation induction in women with PCOS.

REFERENCES

1. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med. 2010;8:41.
2. Saad AK. Polycystic ovary syndrome: diagnosis and management of related infertility. ObsGynReprod Med. 2009;19(10):263–70.
3. Turner KA. Polycystic ovary syndrome: update on treatment options and treatment considerations for the future.Clin Med Insights Womens Health.2011:467–81.

4. Vause TD, Cheung AP, Sierra S, Claman P, Graham J, Guillemin JA, et al. Ovulation induction in polycystic ovary syndrome. *J ObstetGynaecol Can*. 2010;32(5):495-502.
5. Begum MR, Fedrous J, Begum A, Quadir E. Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. FertilSteril. 2009;92(3):853–57.
6. Jirege PR, Patill RS. Comparison of endocrine and ultrasound profiles during ovulation induction with clomiphene citrate and letrozole in ovulatory volunteer women. FertilSteril. 2010;93(1):174–83.
7. Johnson N. Metformin is a reasonable first-line treatment option for non-obese women with infertility related to anovulatory polycystic ovary syndrome--a meta-analysis of randomised trials. Aust N Z J ObstetGynaecol. 2011;51:125-9.
8. Nestler JE. Metformin for the treatment of the polycystic ovary syndrome. N Engl J Med. 2008;358:47–54.
9. Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. Int J Womens Health. 2011; 3: 25–35.
10. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Obstet Gynecol. 2010;115(5):1063–70.
11. Otta CF, Wior M, Iraci GS, Kaplan R, Torres D, Gaido MI, et al. Clinical, metabolic, and endocrine parameters in response to metformin and lifestyle intervention in women with polycystic ovary syndrome: a randomized, double-blind, and placebo control trial. *GynecolEndocrinol.* 2010;26(3):173-8.
12. Sangeeta S. Metformin and pioglitazone in polycystic ovarian syndrome: a comparative study. J ObstetGynaecol India. 2012;62(5):551–56.
13. Tang T, Lord JM, Norman RJ. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2012;5:CD003053.
14. Ota H, Goto T, Yoshioka T, Ohyama N. Successful pregnancies treated with pioglitazone in infertile patients with polycystic ovary syndrome. FertilSteril. 2008 Sep;90(3):709-13.
15. Li XJ, Yu YX, Liu CQ, Zhang W, Zhang HJ, Yan B, Wang LY, et al. Metformin vs thiazolidinediones for treatment of clinical, hormonal and metabolic characteristics of polycystic ovary syndrome: a meta-analysis.ClinEndocrinol (Oxf). 2011 Mar;74(3):332-9.
16. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. BMJ. 2003;327:951–53.
17. Aroda VR, Ciaraldi TP, Burke P. Metabolic and hormonal changes Induced by pioglitazone in polycystic ovary syndrome: a randomized, placebo-controlled clinical trial. J ClinEndocrinolMetabol. 2009;94:469–76.
18. Brettenthaler N, De Geyter C, Huber PR, Keller U. Effect of the insulin sensitizer pioglitazone on insulin resistance, hyperandrogenism, and ovulatory dysfunction in women with polycystic ovary syndrome. J ClinEndocrinolMetab 2004;89(8):3835–40.
19. Glueck CJ, Moreira A, Goldenberg N, et al. Pioglitazone and metformin in obese women with polycystic ovary syndrome not optimally responsive to metformin. Hum Reprod 2003;18:1618–25.