Comparative Efficacy of Myo-Inositol and Metformin in Polycystic Ovary Syndrome Management: A Randomized Controlled Trial in a Local Setting

ABSTRACT

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most frequent endocrinopathy in reproductive-aged women, mainly characterized by oligoanovulation (oligomenorrhea) and hyperandrogenism. Insulin resistance represents a major pathophysiological feature of the syndrome and, therefore, insulin-sensitizing agents (metformin and thiazolidinediones) have been applied in PCOS women. So we want to conduct this study to find the more efficacious drug in resolution of PCOS through decrease in LH/FSH in local setting.

OBJECTIVES

To compare the mean LH/FSH ratio with myo-inositol versus metformin for management of females with polycystic ovarian syndrome.

SUBJECTS AND METHODS

100 patients of PCOS (Polycystic ovarian syndrome) meeting the inclusion criteria were included in the study. The patients were randomly allocated in two groups by lottery method. Patients in Group A were started upon metformin therapy and group B on myoinositol. All the patients were assessed for efficacy both the drugs. Data was collected on proforma and analyzed in SPSS version 10.0. P-value ≤ 0.05 was considered significant.

Results:

A total of **100** patients were recruited for study. These were randomly distributed into two groups of **50** patients in each group, A & B.

In A-group age range was **18** years to **35** years. Mean age was **26.04** years**±4.69SD**, while in B-group age range was **19** years to **35** years. Mean age was **25.70** years**±4.10SD**. There was no significant difference of age in two groups with **p value= 0.612**

LH/FSH ratio wise comparison shows that Group A have average LH/FSH ratio of 2.00±0.899SD while in Group B, it was 1.90±0.48SD observed which was statistically insignificant with p-value = 0.718

Conclusion:

Both the therapy have shown insignificance results in term of LH/FSH Ratio in patients with Polycystic ovarian syndrome.

Key words:

Polycystic ovarian syndrome, efficacy, metformin, myoinositol

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age. More than 30% of women with PCOS are obese (body mass index–BMI>30 kg/m^2), reflecting primarily visceral adiposity. Obesity is a prominent feature of PCOS, occurring in 40-50% of PCOS patients. Prevalence of PCOS is increased in overweight and obese women when compared to their lean counterparts. The prevalence rates of PCOS in underweight, normal-weight, overweight, and obese women are 8.2%, 9.8%, 9.9% and 9.0% respectively. Prevalence rates are 12.4% and 11.5% in women with BMI 35-40 kg/m^2 and greater than 40 kg/m^2.[1]

Both treatments induced an improvement in insulin sensitivity documented by the change of menstrual pattern during the euglycaemic hyperinsulinaemic clamp, though these differences did not reach the statistical significance.[2] Results of a trial reported that taking myo-inositol, compared with metformin, for 12weeks in PCOS patients with hyperinsulinism and normoinsulinism had beneficial effects on total testosterone, modified Ferryman Gallway scores, serum hs-CRP levels, and gene expression of IL-1, but did not affect other hormonal profiles, NO levels, or gene expression of IL-8 and TNF-α.[3]

One trial also concluded that both metformin and MYO significantly reduced the insulin response to OGTT and improved insulin sensitivity. Metformin treatment was also associated with a significant decrease in LH and oestradiol levels, androgens and anti-müllerian hormone levels. None of these clinical and hormonal changes were observed during MYO administration. Thus both treatments improved the glyco-insulinaemic features of obese PCOS patients, but only metformin seems to exert a beneficial effect on the endocrine and clinical features of the syndrome.[4-6]

One study conducted on 60 females, mean LH/FSH was 1.99±0.38 with myoinositol and 1.72±0.20 with metformin. The difference was significant (P<0.05).[7] Another study showed that mean LH/FSH was 2.11±0.44 with myoinositol (n=37) and 1.71±0.28 with metformin (n=35). The difference was significant (P<0.05).[8] But one study showed that mean LH/FSH was 2.17±0.92 with myoinositol (n=26) and 2.43±1.67 with metformin (n=28). The difference was insignificant (P>0.05).[9]

The rationale of this study is to compare the outcome of myo-inositol versus metformin for management of females with PCOS syndrome. Through literature, it has been noticed that serum

LH/FSH was less with metformin as compared to myo-inositol. But controversial results have been obtain through literature. Moreover, those studies were conducted on small sample size and there is no local study available in literature which could help us in implementing the more favorable and reliable drug. So we want to conduct this study to find the more efficacious drug in resolution of PCOS through decrease in LH/FSH in local setting. This will help to improve our practice and helps the PCOS females to attain normal menstrual functionality.

DATA COLLECTION PROCEDURE

After taking approval from hospital ethical committee, this randomized controlled trial was carried out over 100(50 cases in each group was calculated with Confidence level = 95%, Power of study = 90% and magnitude of LH/FSH ratio i.e. 1.72 ± 0.20[7] with metformin and 1.99 ± 0.38[7] with myo-inositol for females with PCOS using WHO software for sample size determination) females which were enrolled in the study from OPD of Department of Obstetrics & Gynecology, Khyber Teaching hospital, Peshawar Aug 11, 2020 to Feb 10, 2021.

After obtaining informed consent and demographic information (name, age, BMI, marital status, parity of married females, duration of symptoms) were recorded. Then all females were randomly divided in two groups by using lottery method. At baseline, blood sample were obtained by using 3cc BD syringe and were sent to the laboratory of the hospital for assessment of LH and FSH level. Ratio was calculated at baseline. In group A, metformin (850mg BD) was prescribed. In group B, myoinositol (500mg TD) was prescribed. All females were followed-up for 12weeks. Then after 12 weeks, again blood sample were obtained by using 3cc BD syringe and were sent to the laboratory of the hospital for assessment of LH and FSH level. Reports were assessed and LH/FSH ratio were calculated and noted.

Pregnancy with PCOS, history of previous treatment for PCOS, Medical disorder like hypertension, diabetes, cardiac problem, renal insufficiency and anemia patients are excluded as its act as confounders and will make the study results biased.

All this information were entered and analyzed through SPSS version 21. Independent sample t-test was used and P-value$\leq$0.05 was taken as significant.

RESULTS

This study was conducted to compare the mean LH/FSH ratio between metformin therapy and myo-inositol in polycystic ovarian syndrome patients in department of Obstetrics &Gynecology, poly clinic hospital Islamabad. Then patients were divided into two groups randomly through lottery method. Group A was started upon metformin therapy and group B on myo-inositol. Patients were then called for follow up at 12 weeks then patients were again interrogated for improving her symptoms like regulating menstrual cycles and LH/FSH ration at follow ups.

A total of **100** patients were recruited for study. These were randomly distributed into two groups of **50** patients in each group, A & B.

In A-group age range was **18** years to **35** years. Mean age was **26.04** years**±4.69SD**, while in B-group age range was **19** years to **35** years. Mean age was **25.70** years**±4.10SD**. There was no significant difference of age in two groups with **p value= 0.612**. Majority of the patients were observed of age having 26-30 years of age in both the groups. Overall age in both the groups was 25.9years ±4.38SD.

LH/FSH ratio wise comparison shows that Group A have average LH/FSH ratio of 2.00±0.899SD while in Group B, it was 1.90±0.48SD observed which was statistically insignificant with p-value = 0.718 using independent t-test. Table 1

Insignificant results were found when Parity, marital status and BMI were stratified and shows that all of them are insignificant except for BMI of more than 24 kg/m^2 with p-value=0.01. Table 2

Table 2:

COMPARISON OF LH/FSH RATIO IN BOTH THE GROUPS

	Group	N	Mean	Std. Deviation	p-value
LH/FSH	A	50	2.0082	.89960	0.718
	B	50	1.9006	.48276	

Table 2:

LH/FSH RATION STRATIFICATION OVER PARITY, MARITAL STATUS AND BMI

			LH/FSH			P-Value
		Group	Count	Mean	Standard Deviation	
Parity	<= 1.00	A	44	2.02	.92	0.4452
		B	45	1.90	.50	
	2.00+	A	6	1.94	.75	0.9344
		B	5	1.91	.26	
Marital Status	Married	A	33	2.00	.89	0.3813
		B	36	1.85	.48	
	Unmarried	A	17	2.03	.95	0.9716
		B	14	2.04	.47	
BMI (kg/ m^2)	<= 24.00	A	28	1.72	.78	0.1973
		B	30	1.95	.55	
	25.00+	A	22	2.38	.92	0.0165
		B	20	1.83	.36	

DISCUSSION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in premenopausal women with a prevalence rate of 5.10 %.[10] Evidence suggests that insulin resistance and hyperinsulinaemia are associated with ovarian hyperandrogenism and menstrual irregularities in PCOS.

The primary etiology of PCOS has not yet been determined, but it is known that many metabolic disturbances occur within this disease and cause associated symptoms. It is hypothesized that dysfunction of glucose and insulin metabolism leads to increasing symptoms of androgen excess, which in turn, results in worsening of metabolic function and obesity. Insulin resistance leads to hyperinsulinemia,[11] which promotes secretion of androgens from the ovaries and decreases the amount of serum sex hormone-binding globulin (SHBG); therefore, serum free testosterone is elevated. Other hormones such as luteinizing hormone (LH), follicle stimulating hormone (FSH), estrogen and other androgenic derivatives are negatively affected.[12] Ovarian follicle growth and maturation is altered by hyperinsulinemia and androgen excess,[13] causing menstrual irregularity and infertility.

Treatment with metformin resulted in significant improvements in insulin sensitivity in women with PCOS. Improved insulin-stimulated glucose utilizationwas observed at physiological and supra-physiological insulin concentrations, confirming the capacity of metformin to improve insulin action in the presence of normal and elevated insulin concentrations. In Evanthia Diamanti—Kandarakis[13] and others reports that the return to normal menstruation occurs in over 50% of subjects of PCOS, treated with metformin and the reporting of two spontaneous pregnancies also. Metformin was used as first insulin sensitizing drug in treating PCOS patients by Velazquez[14] and their colleagues and reported in an observational study a significant improvement in menstrual regularity and reduction in circulating androgen levels.

Myo-inositol (MI) is one stereoisomer of a C_6 sugar alcohol that belongs to the inositol family[15,16]. It is the precursor of inositol triphosphate, acting as an intracellular second messenger and regulating a number of hormones such as thyroid-stimulating hormone, follicle-stimulating hormone (FSH) and insulin[17].

Vincenzo et al. compared the effect of metformin and myoinositol. Metformin group and myoinositol both showed significant improvement in regularization of menses and reduction in FG score and BMI, insulin glucose and HOMA, testosterone, LH.[18] But the study failed to establish superiority of one drug over the other.

A study conducted by Tang and colleagues[19] assessed whether lifestyle changes alone or in combination with metformin (an insulin sensitizer) are associated with superior endocrine, anthropometric, and menstrual cycle characteristics among PCOS women. Patients in both groups showed similar improvements in their menstrual cyclicity with 52.2% improvement in the metformin group and 58.1% in the placebo group. Significant weight loss was achieved in both groups. The loss was greater in the metformin group, but the difference was not significant. Androgen levels were reduced in the metformin group only. Glucose and insulin levels and insulin sensitivity did not change with either approach. Spontaneous pregnancy rates were similar in both groups.

Another study shows that myoinositol has resulted in a significant reduction of more parameters than metformin. With myoinositol there was a reduction in weight, BMI, LH/FSH ratio, acne and hirsutism. Metformin has resulted in a decrement of body weight, BMI and acne only. This finding perhaps supports the hypothesis that myoinositol works at the ovarian level and brings about a change in the hormonal mileu, decreases the LH/FSH ratio and hence improves the oocyte quality.[20]

CONCLUSION

There was insignificant difference between the myo-inositol and metformin for females with PCOS. PCOS is not only a health hazard but also an economic burden. Based on the above observations it can be said that, since the clinical features of PCOS are heterogeneous, they have to be investigated accordingly, for selection of appropriate treatment modality. Early identification of high risk cases and timely therapeutic intervention can halt this on-going process and prevent long term complications. The above-mentioned findings show a more favorable response of PCOS women to myoinositol compared to metformin. But more studies with a bigger sample size and longer follow-up are required to establish the accurate results.

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