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ROLE OF METFORMIN VERSUS MYO-INOSITOL IN WOMEN WITH POLYCYSTIC OVARY SYNDROME (PCOS)

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder among women of reproductive age, often associated with metabolic, reproductive, and anthropometric abnormalities due to underlying insulin resistance. This study aimed to compare the efficacy of myoinositol and metformin—two insulin-sensitizing agents—in the management of PCOS. A randomized controlled trial was conducted over eight months at the Department of Obstetrics & Gynaecology, SMBBMU, Larkana, Pakistan. Eligible patients were randomly assigned to receive either myoinositol or metformin and were followed up at two-month intervals over a six-month treatment period. The mean age in the myoinositol group was 26.6 ± 5.1 years, while in the metformin group it was 27.1 ± 4.9 years. Myoinositol was found to be effective in 23 (65.7%) patients compared to 9 (25.7%) in the metformin group, with a statistically significant difference ($p = 0.001$). These findings suggest that myoinositol may offer superior efficacy compared to metformin in managing PCOS. However, further research is warranted to account for potential residual confounding factors and to confirm these outcomes in larger populations.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinological disorders in women in the reproductive age group, with an estimated incidence of 5-10% [1]. More than 30% of women with PCOS are obese (body mass index- BMI>30 kg/m2), reflecting primarily visceral adiposity [1-2]. Obesity is a prominent feature of PCOS, occurring in 40-50% of PCOS patients [2,3]. The 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/m2 and greater than 40 kg/m2 [4].

Increased adiposity, particularly visceral adiposity that is reflected by an elevated waist circumference (>88 cm) or waist-to-hip ratio (WHR), has been associated with hyperandrogenemia, insulin resistance, glucose intolerance, and dyslipidemia [5]. Genes that are involved in the pathogenesis of PCOS include genes associated with steroidogenesis, regulation of gonadotropin secretion, effects of insulin, obesity, factors regulating the body's energy expenditure, and genes associated with chronic inflammation [6]. PCOS women tend to have an increased BMI and WHR, i.e., abdominal (visceral) obesity [7,8]. A systematic review of randomized controlled trials reported the 69.5% efficacy in women belonging to the myoinositol group versus 21% belonging to the metformin group ($p = 0.001$) [9].

Anthropometric parameters suggesting insulin resistance are obesity (increased BMI) and WHR>0.85. Numerous studies have demonstrated a pathogenetic association of PCOS with insulin resistance and hyperinsulinaemia. [9-11]. Metformin and myoinositol, being insulin sensitizers, improve the metabolic, reproductive, and anthropometric parameters, i.e., weight, BMI, and WHR in women suffering from PCOS [12,13]. The efficacy and safety of myoinositol and metformin are already established in various studies. Some studies have shown these drugs' comparable efficacy in improving clinical features. A randomized comparative study conducted by Riju Angik et al reported ovulation (36.84% v/s 33.33%) in the myoinositol versus metformin group, respectively, in women with PCOS [12]. MI plays an important role as the structural basis for many secondary messengers, including the synthesis of phosphatidylinositol 3- 3-kinase (PI 3-kinase), a key messenger to improve insulin sensitivity and thereby reduce insulin resistance and achieve ovulation in 72% of women with PCOS [8-12].

Women with PCOS are also known to have a defect in their insulin-signaling pathways, which are heavily dependent upon inositol-containing substances (phospholipid mediators). A systematic review of randomized controlled trials reported the 69.5% efficacy in women belonging to the myoinositol group versus 21% belonging to the metformin group ($p = 0.001$) [10-14]. Insulin directly promotes ovarian steroidogenesis and inhibits liver release of the sex hormone binding globulin (SHBG) and production of insulin-like growth factor binding protein 1 (IGFBP-1). Increased concentrations of IGF-1 additionally promote ovarian release of androgens [14]. Though studies have compared the efficacy of myoinositol versus metformin in women with polycystic ovary syndrome internationally, very few and outdated studies are available in our local context. Due to differences in race, poverty, environment, education, and socioeconomic status compared to Western countries, we might observe different results in our studies. As a result, this study offers new information to gynecologists that can influence clinical practice. Furthermore, this study provides insights into which treatment is superior and recommends one as the first choice of treatment. In addition, this study will emphasize early diagnosis and management to improve care for women with polycystic ovary syndrome.

MATERIAL & METHODS

STUDY DESIGN

Randomized Control Trial.

STUDY SETTING

Department of Obstetrics & Gynaecology, SMBBMU, Larkana

DURATION OF STUDY

Eight months after the approval of the synopsis on October 29, 2020, to June 28, 2021.

SAMPLE SIZE

Sample size was calculated via W.H.O sample size calculator by using the efficacy (69.5% v/s 21%) [9] in women belonging to the myoinositol group versus the metformin group, respectively. Level of significance $a=5\%$, Power of test $(1-\beta) = 80\%$, then the calculated sample size was $n=16$ in each group. By keeping the chance of lost to follow in mind included $n=35$ patients in each group.

SAMPLING TECHNIQUE

Non-Probability, Consecutive Sampling.

SAMPLE SELECTION

INCLUSION CRITERIA:

- Women in the reproductive age group, 16—40 years.
- Infertile females with polycystic ovarian syndrome by operational definition.

EXCLUSION CRITERIA

- Patients are already on other drug treatments for PCOS.
- Deranged kidney.
- Patients who have already received any medical or surgical treatment for any thyroid disorder.
- Hypersensitivity to myoinositol.

DATA COLLECTION

Data collection was started after approval of the synopsis from the ethical committee of the hospital and CPSP. Patients were randomly allocated to treatment with either myoinositol (35 in myoinositol group) or metformin (35 in metformin group), by using computer-generated sequential numbers placed in sealed envelopes and opened only before the commencement of the study. The study was conducted in a single blind fashion. Prior to enrolment, a written informed consent was also obtained. Women who met the inclusion criteria were subjected to treatment according to the randomization number. The randomization list kept concealed until the study completed. Participants of myoinositol group received myoinositol 1 gm once daily and, of metformin group received 500 mg metformin tablet three times daily. All the patients were called for follow up visits every two months and after 6 months of drug therapy. Final outcome variable i.e. efficacy in terms of ovulation and menstrual regularity was documented by researcher herself under the supervision of consultant having > 5 year of experience. All the collected information was entered into the predesigned proforma (attached).

DATA ANALYSIS

Data was entered and analyzed in the Statistical Package for Social Sciences (SPSS Version 20.0). Mean and standard deviation were calculated for quantitative variables like age, weight, height, and BMI. Frequencies and percentages were calculated for efficacy. The chi-square test was used to compare the efficacy in both groups. Consider a two-sided $P \leq 0.05$ as a criterion for statistical significance. Both groups were compared by age, and BMI-wise stratification to control the confounders/effect modifiers by using the Chi-square test to see the impact of these on the outcome variable, considered two-sided $P < 0.05$ as significant.

RESULTS

In this study, 70 patients were divided randomly by the envelope method into two equal groups, A (myoinositol) and B (metformin), to compare the role of myoinositol versus metformin in women with polycystic ovary syndrome, and the results were analyzed as:

Mean±SD of age in the myoinositol group was 26.6±5.1 with C. I (24.84--- 28.35) and the metformin group were 27.1±4.9 with C. I (25.41- 28.78) years, as shown in TABLE 1.

Mean±SD of height in the myoinositol and metformin groups was 1.60±1.2 and 1.58±1.1 with C. I (1.18----2.01) and (1.20----1.95) meters, respectively, as shown in TABLE 2.

Mean±SD of weight in myoinositol was 62.1±9.2 with C. I (58.93---- 65.26) and the metformin group were 61.6±8.5 with C. I (58.68----64.51) kg, as shown in TABLE 3.

Mean±SD of body mass index in the myoinositol and metformin group was 25.9±4.9 and 26.2±5.0 with C. I (24.21----27.58) and (24.48----27.91) kg/m2, respectively, as shown in TABLE 4. Myoinositol was found to be effective in 23 (65.7%) patients while metformin was found to be effective in 09 (25.7%), and the P value was found to be highly significant, i.e., (P=0.001 as shown in TABLE 5. Stratification of age group and body mass index was done to assess the statistical difference between both groups from **(TABLE 6-7)**.

TABLE # 1 DESCRIPTIVE STATISTICS OF AGE

n=70

AGE [Years]		n	MINIMUM	MAXIMUM	MEAN	±SD	95% C. I
GROUP	Myoinositol	35	16	40	26.6	5.1	24.84-- 28.35
	Metformin	35	16	40	27.1	4.9	25.41-- 28.78

TABLE # 2 DESCRIPTIVE STATISTICS OF HEIGHT

n=70

HEIGHT [Meters]		N	MINIMUM	MAXIMUM	MEAN	±SD	95% C. I
GROUP	Myoinositol	35	1.38	1.82	1.60	1.2	1.18---2.01
	Metformin	35	1.39	1.82	1.58	1.1	1.20---1.95

TABLE # 3 DESCRIPTIVE STATISTICS OF WEIGHT

n=70

WEIGHT [kg]		n	MINIMUM	MAXIMUM	MEAN	±SD	95% C. I
GROUP	Myoinositol	35	45	100	62.1	9.2	58.93-- 65.26
	Metformin	35	45	105	61.6	8.5	58.68-- 64.51

TABLE # 4

DESCRIPTIVE STATISTICS OF BODY MASS INDEX n=70

BMI [kg/m^2]		n	MINIMUM	MAXIMUM	MEAN	±SD	95% C. I
GROUP	Myoinositol	35	15	34	25.9	4.9	24.21-- 27.58
	Metformin	35	15	34	26.2	5.0	24.48-- 27.91

TABLE # 5

COMPARISON OF EFFICACY BETWEEN GROUPS n=70

GROUP	EFFICACY		P-VALUE
	Yes	No	
Myoinositol	23 (65.7%)	12 (34.3%)	0.001
Metformin	9 (25.7%)	26 (74.3%)	

Applied Chi-Square test

TABLE # 6

STRATIFICATION OF AGE GROUPS WITH EFFICACY BETWEEN GROUPS

n=70

AGE GROUP [In Years]		EFFICACY		P-VALUE
		Yes	No	
16– 30	Myoinositol	17 (65.4%)	9 (34.6%)	0.001
	Metformin	4 (16.7%)	20 (83.3%)	

>30	Myoinositol	6 (66.7%)	3 (33.3%)	0.311
	Metformin	5 (45.5%)	6 (54.5%)	

Applied Fisher's Exact test

TABLE # 7
STRATIFICATION OF BODY MASS INDEX WITH EFFICACY BETWEEN GROUPS
n=70

BMI [In kg/m2]		**EFFICACY**		**P-VALUE**
		Yes	**No**	
15– 24	Myoinositol	19 (76.0%)	6 (24.0%)	0.003
	Metformin	7 (31.8%)	15 (68.2%)	
>24	Myoinositol	4 (44.4%)	5 (55.6%)	0.155
	Metformin	2 (15.4%)	11 (84.6%)	

Applied Fisher's Exact test

DISCUSSION

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, prevalent across different populations around the world. This syndrome was first described by Stein and Leventhal in 1931. It is a disorder characterized by excessive secretion of androgens by the ovaries, oligomenorrhoea, anovulation/oligoanovulation, and insulin resistance, and with variable clinical manifestations that include irregular menstrual cycles, hirsutism, alopecia, and acne [15]. PCOS increases women's risk of infertility, dysfunctional uterine bleeding, endometrial carcinoma, as well as insulin resistance, dyslipidemia, and hypertension (all risk factors for cardiovascular disease – CVD). The potential increased risk of CVD may be related to the higher incidence of metabolic syndrome in this population [16]. PCOS is characterized by chronic anovulation and is the most common cause of excess androgen production [17]. It is also the most common hormonal disturbance that can

underlie hirsutism (over half of cases), acne, seborrhea, and pattern alopecia [18]. On the other hand, each of these symptoms is a variably expressed skin manifestation of androgen excess, so any or all may be absent in patients with the moderate degree of hyperandrogenemia that typifies PCOS [19]. PCOS is the most common cause of infertility, ovarian dysfunction and menstrual irregularity, affecting 5%–10% of women in reproductive age [20]. Both the aetiology and diagnosis of the syndrome are controversial. Indeed, the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine sponsored a Consensus Meeting in Rotterdam (2003) [21,22], to reach a general agreement of the scientific community on diagnostic criteria for this syndrome. Although nowadays the criteria established in Rotterdam are widely accepted, they leave out a crucial condition related to PCOS: insulin resistance. Several studies have reported that insulin resistance is common in PCOS women, regardless of the body mass index (BMI). Indeed, hyperinsulinaemia due to insulin resistance occurs in approximately 80% of women with PCOS and central obesity, as well as in 30%–40% of lean women diagnosed with PCOS [23,24]. The exact cause of the insulin resistance observed in PCOS women is unknown, although a post-receptor defect, which could affect glucose transport, has been proposed [25,26]. Insulin resistance is significantly exacerbated by obesity, and it is a key factor in the pathogenesis of anovulation and hyperandrogenism [24,27]. The importance of insulin resistance in PCOS is also suggested by the fact that insulin-sensitizing compounds, such as metformin, pioglitazone, and troglitazone, have been proposed as treatment to solve the hyperinsulinemia-induced dysfunction of ovarian response to endogenous gonadotropins. Rescuing the ovarian response to endogenous gonadotropins reduces hyperandrogenemia, re-establishes menstrual cyclicity and ovulation, increasing the chance of a spontaneous pregnancy [28–30]. In particular, metformin induces a reduction of total and free testosterone concentrations [31]. However, commonly used insulin-sensitizing drugs, like metformin, can induce gastrointestinal side effects [32], possibly resulting in reduced patient compliance [32]. Further studies have suggested that impairment in the insulin pathway could be due to a defect in the inositolphosphoglycans (IPGs) second messenger [33,34]. IPGs are known to have a role in activating enzymes that control glucose metabolism [35,36]. In PCOS women, a defect in tissue availability or altered metabolism of inositol or IPGs mediators may contribute to insulin resistance [37]. Inositol belongs to the vitamin B complex. Epimerization of the six hydroxyl groups of inositol leads to the formation of up to nine stereoisomers, including myo-

inositol (MYO) and D-chiroinositol (DCI); both stereoisomers were used as insulin sensitizer drugs in the treatment of PCOS [38–42]. Human adults consume approximately 1 g of inositol (mainly MYO) per day in different biochemical forms [37]. Circulating free MYO is taken up by most tissues by a membrane-associated sodium-dependent inositol co-transporter; inositol uptake is inhibited by glucose [43]. In particular, it was shown that MYO had 10 times more affinity for the transporter compared to DCI [44]. Data from other groups have shown that DCI is synthesized by an epimerase that converts MYO into DCI, with each tissue having its particular conversion rate, likely due to the specific needs for the two different molecules [45,46]. In particular, it was shown that the DCI to mass index (MI) ratio was itself insulin dependent. In fact, in subjects suffering from type 2 diabetes, the DCI/ MI ratio was reduced [34,34,46,47], and less DCI was synthesized due to a reduction in epimerase activity [33,34,46,47]. All of these studies were performed on insulin-sensitive tissues, such as muscle and liver. However, unlike tissues such as muscle and liver, ovaries do not become insulin resistant [48–50]. In our study, the mean age in the myoinositol group was 26.6±5.1 and the metformin group was 27.1±4.9 years. The study of Nehra J, et al [14] noted mean age in myoinositol and metformin groups as 23.8±0.69 and 23.26±1.03, respectively. Shokrpour M, et al [51] noted age as 28.3±4.9 and 27.7±3.2 years in the myoinositol and metformin groups, respectively. Another study found to have a mean age in myoinositol group as 21.6±6.6 and 22.3±6.0 in metformin group. Agrawal A, et al[53] reported as 28.35±2.74 and 28.12±3.34 years, whereas Nehra JY, et al [54] found as 23.8±0.69 and 23.26±1.03 in myoinositol and metformin groups. In this study, mean height in the myoinositol and metformin groups was 1.60±1.2 and 1.58±1.1 meters, respectively. Shokrpour M, et al [51] reported height as 161.4±3.3 in the myoinositol group and 161.9±4.8 cm in the metformin group. In the current study, the mean weight in the myoinositol group was 62.1±9.2 and the metformin group was 61.6±8.5 kg. Nehra J, et al further noted weight as 63.96±0.90 in the myoinositol group, whereas 63.58±1.88 was noted in the metformin group [14]. The study of Shokrpour M, et al further recorded weight in the myoinositol and metformin groups as 73.2±8.9 and 71.5±8.7 kg, respectively [51]. The study of Nehra JY, et al [54] noted as 63.96±0.90 in the myoinositol group, and in the metformin group it was 63.58±1.88 kg/m2.

In the present study, the mean body mass index in the myoinositol and metformin groups was 25.9±4.9 and 26.2±5.0 kg/m2, respectively. The body mass index in the myoinositol and metformin groups was recorded as 25.31±0.40 and 24.96±0.68 kg/m2 [14]. Shokrpour M, et al

[51] documented body mass index as 28.1±3.1 and 27.3±3.3 kg/m2 in myoinositol and metformin groups. The study of Fruzzetti F, et al recorded as 27.3±4.5 and 28.4±5.2 kg/m2 in myoinositol and metformin groups [52]. Agrawal A, et al also noted to have a body mass index of 27.71±3.60 and 27.38±3.92 kg/m2 [53] while Nehra JY, et al documented a BMI of 26.45±0.41 in the myoinositol group and 26.09±0.76 in the metformin group [54]. In a recent study, myoinositol was found to be more effective in 23 (65.7%) patients as compared to metformin, where efficacy was noted in 09 (25.7%), and the P value was found to be highly significant, i.e., P=0.001. Unfer V, et al [9] recorded the efficacy in 16 (69.5%) women belonging to the myoinositol group and 04 (21%) belonging to the placebo group with a significant P value of 0.001. Fruzzetti F, et al [52] noted to have efficacy in 53% of the women in the metformin group and in 44% of women in the myoinositol group, while Agrawal A, et al [53] recorded as 63.3% and 33.3%. In our study, stratification of confounders/effect modifiers with respect to age group, a significant difference was noted in 16–30 (P=0.001) and an insignificant difference was documented in >30 (P=0.311). In this study, stratification of confounders/effect modifiers with respect to body mass index, a significant difference was noted in 15–24 (P=0.003) and an insignificant difference was documented in >24 (P=0.15).

CONCLUSION

It is to be concluded that a significant difference was noted in terms of efficacy between myoinositol versus metformin in women with polycystic ovary syndrome, but we cannot rule out residual confounders. More randomized clinical trials are necessary to compare the effectiveness of these drugs, probably with a larger sample size and with more parameters in multiple study centers in Pakistan are needed to validate the findings of the present study.

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