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COMPARISON OF MYO-INOSITOL ALONE VERSUS IN COMBINATION WITH CLOMIPHENE CITRATE FOR MANAGEMENT OF FEMALES PRESENTING WITH POLYCYSTIC OVARIAN SYNDROME

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Abstract:
Objectives: To compare the frequency of ovulation with myo-inositol alone versus in combination with clomiphene citrate for management of females presenting with polycystic ovarian syndrome.
Materials and Methods: In this RCT study, we enrolled a total of 500 females. Then females were randomly divided into two groups by using the lottery method. In group A, females were given 2g of myoinositol before breakfast and in group B, females were given 2g of myoinositol plus clomiphene citrate 50mg tablet before breakfast for 12 weeks. Females were followed up for 12 weeks. Then females underwent color Doppler ultrasonography for assessment of ovulation. If follicle of size ≥21mm ovulate from ovary on ultrasound, then ovulation was labeled. All this information was recorded through pre-designed proforma. The collected data was analyzed statistically by using SPSS version 21**.**
Results: In myoinositol group, the mean age of patients was 30.92±5.91years. In myoinositol plus clomiphene citrate group, the mean age of patients was 30.24±5.85years. After 4 weeks, ovulation was achieved in 39 (15.6%) patients with myoinositol and in 75 (30%) patients with myoinositol plus clomiphene citrate. After 8 weeks, ovulation was achieved in 119 (47.6%) patients with myoinositol and in 153 (61.2%) patients with myoinositol plus clomiphene citrate. After 12 weeks, ovulation was achieved in 154 (61.6%) patients with myoinositol and in 196
(78.4%) patients with myoinositol plus clomiphene citrate. The difference was significant ($p<0.05$).
Conclusion: It was concluded that the combination of myoinositol and clomiphene citrate was more effective in ovulation in females with PCOS.

Keywords: Ovulation, myoinositol, clomiphene citrate, polycystic ovarian syndrome.

INTRODUCTION:

Polycystic ovarian syndrome (PCOS) is a hormonal disorder common among women of reproductive age.(1) It is a complex condition with a variety of possible contributing factors, including genetics, insulin resistance, and hormonal imbalances.(2) The worldwide occurrence of PCOS ranges from 5 to 18%, with Europe having an average incidence of 276.4 cases per 100,000 individuals.(3) In Pakistan, 40.9% of infertile females are affected by PCOS.(4) PCOS presents with diverse clinical manifestations and an unknown cause, contributing to ongoing scientific debate due to its complex pathophysiology and challenges in diagnosis.(5) The diagnosis of PCOS has been a subject of debate in clinical endocrinology.(6) The NIH criteria established in 1990 and the Rotterdam criteria introduced in 2003 provide definitive parameters for diagnosing polycystic ovarian syndrome (PCOS), encompassing oligomenorrhea/anovulation, hyperandrogenism, and the presence of polycystic ovaries characterized by 12 or more follicles measuring 2–9 mm in each ovary. When evaluating the management of PCOS, it is crucial to consider the efficacy of different treatment modalities. (7, 8)

When comparing myo-inositol alone to its combination with clomiphene citrate for managing polycystic ovarian syndrome (PCOS) in females, several factors should be considered. Clomiphene citrate primarily induces ovulation by stimulating hormone release from the pituitary gland, while myo-inositol may improve ovulatory function by addressing insulin resistance and hormonal imbalances.(9) Myo-inositol also improves metabolic parameters, whereas clomiphene citrate does not directly target metabolic abnormalities.(10, 11) Studies suggest improved pregnancy rates with either treatment alone or in combination, potentially offering synergistic effects, especially for non-responders to clomiphene citrate. However, clomiphene citrate poses a higher risk of multiple gestation pregnancies, which myo-inositol may help mitigate by enhancing ovulation quality.(12) Both treatments are generally well-tolerated, but individual responses vary. Ultimately, treatment choice should consider patient characteristics, goals, and response to therapy, warranting consultation with a healthcare provider experienced in PCOS management. The study aims to address the effectiveness and potential synergistic benefits of two treatment approaches for managing polycystic ovarian syndrome (PCOS) in females: myo-inositol alone versus myo-inositol in combination with clomiphene citrate. This research is crucial due to the high prevalence and varied clinical manifestations of PCOS, along with the ongoing debate regarding optimal treatment strategies. By comparing these two treatment modalities, the study seeks to provide evidencebased insights into their respective efficacy in improving ovulation.

Objective:

To compare the frequency of ovulation with myoinositol alone versus in combination with clomiphene citrate for management of females presenting with polycystic ovarian syndrome.

MATERIALS AND METHODS:

Study Design: Randomized Controlled Trial.

Study setting: Department of Obstetrics & Gynecology, Lady Willingdon Hospital, Lahore.

Duration of the study: The duration of the study was 6 months from 15th Jun 2018 to 15th Dec 2018.

Inclusion Criteria:

• Married women aged between 20 and 40 years, exhibiting symptoms consistent with Polycystic Ovary Syndrome (PCOS).

Exclusion Criteria:

• Women experiencing systemic issues such as hypertension (blood pressure ≥140/90 mmHg) or diabetes (blood sugar level >186 mg/dL as recorded in medical records), renal dysfunction (creatinine level >1.2 mg/dL), liver impairment (elevated ALT >40 IU or AST >40 IU), or anemia (hemoglobin <10 mg/dL).

• Women with a history of malignancy or metastatic disease, or those who have undergone previous treatment for cancer.
• Women with a history of medical treatment for PCOS.
• Patients with secondary infertility,

Methods:
After obtaining approval from the hospital's ethical committee, 500 eligible females were recruited from the outpatient department (OPD) of Lady Willingdon Hospital, Lahore, for participation in the study. Informed consent was obtained from all participants. Demographic details including name, age, BMI, and duration of symptoms were recorded for each participant. All the enrolled patients were randomly assigned to two groups using a lottery method. Group A received 2g of myoinositol before breakfast, while Group B received 2g of myoinositol plus a 50mg tablet of clomiphene citrate before breakfast, both administered daily for a duration of 12 weeks. Participants were then followed up in the OPD every four weeks for a total of 12 weeks. During each visit, they underwent color Doppler ultrasonography to assess ovulation. The ultrasounds were performed by a consultant radiologist with a minimum of 4 years of residency experience, under the supervision of the researcher. Ovulation was considered to have occurred if a follicle of size ≥21mm was observed to ovulate from the ovary on ultrasound, according to the predefined operational definition. All relevant information, including demographic data and ultrasound findings, was meticulously recorded using a pre-designed proforma. The collected data was analyzed statistically by using SPSS version 21.

RESULTS:
In myoinositol group, the mean age of patients was 30.92±5.91years. In myoinositol plus clomiphene citrate group, the mean age of patients was 30.24±5.85years. In myoinositol group, the mean BMI of patients was 26.72±4.56kg/m2. In myoinositol plus clomiphene citrate group, the mean age of patients was 26.77±4.86kg/m2. In myoinositol group, the mean duration of symptoms was 6.24±3.88years. In myoinositol plus clomiphene citrate group, the mean duration of symptoms was 6.30±3.78years. In this study, ovulation was achieved in 114 (22.8%) patients after 4weeks, in 272 (54.4%) patients after 8weeks and in 350 (70%) patients after 12weeks. After 4 weeks, ovulation was achieved in 39 (15.6%) patients with myoinositol and in 75 (30%) patients with myoinositol plus clomiphene citrate. The difference was significant ($p<0.05$). After 8 weeks, ovulation was achieved in 119 (47.6%) patients with myoinositol and in 153 (61.2%) patients with myoinositol plus clomiphene citrate. The difference was significant ($p<0.05$). After 12 weeks, ovulation was achieved in 154 (61.6%) patients with myoinositol and in 196 (78.4%) patients with myoinositol plus clomiphene citrate. The difference was significant ($p<0.05$). Data was stratified for age of patients. In patients aged 2030years, ovulation was achieved in 69 (61.1%) patients with myoinositol and in 98 (75.4%) patients with myoinositol plus clomiphene citrate. The difference was significant ($p<0.05$). In patients aged 31-40years, ovulation was achieved in 85 (62%) patients with myoinositol and in 98 (81.7%) patients with myoinositol plus clomiphene citrate. The difference was significant ($p<0.05$). Data was stratified for BMI of patients. In normal BMI patients, ovulation was achieved in 56 (58.3%) patients with myoinositol and in 77 (80.2%) patients with myoinositol plus clomiphene citrate. The difference was significant ($p<0.05$). In overweight patients, ovulation was achieved in 46 (55.4%) patients with myoinositol and in 58 (74.4%) patients with myoinositol plus clomiphene citrate. The difference was significant ($p<0.05$). In obese patients, ovulation was achieved in 52 (73.2%) patients with myoinositol and in 61 (80.3%) patients with myoinositol plus clomiphene citrate. The difference was insignificant ($p>0.05$). Data was stratified for duration of symptoms. In patients having symptoms from 1-5years, ovulation was achieved in 72 (63.2%) patients with myoinositol and in 96 (78.7%) patients with myoinositol plus clomiphene citrate. The difference was significant ($p<0.05$). In patients having symptoms from 6-10years, ovulation was achieved in 61 (62.2%) patients with myoinositol and in 64 (72.7%) patients with myoinositol plus clomiphene

citrate. The difference was significant (p<0.05). In patients having symptoms from 11 - 15years, ovulation was achieved in 21 (55.3%) patients with myoinositol and in 36 (90%) patients with myoinositol plus clomiphene citrate. The difference was significant (p<0.05).

Table 1: Mean age of all enrolled Patients *(n=500)*

Variables	**Groups**	
	Group A	Group B
Age (Years)	30.92±5.91	30.24±5.85
BMI (kg/m2)	26.72±4.56	26.7±4.86
Duration of symptoms (years)	6.24±3.88	6.30±3.78
	±	±

Table 2: Comparison of ovulation after 8 weeks and 12 weeks in both groups (*n=500)*

	Groups		Chi-Square Test	P-value
	Group A	**Group B**		
Ovulation after 8weeks				
YES	119(47.6%)	153(61.2%)	9.320	0.00
NO	131(52.4%)	97(38.8%)		
Ovulation after 12weeks				
YES	154(61.6%)	196(78.4%)		
NO	96(38.4%)	54(21.6%)	16.800	0.00

Table 3: Comparison of ovulation in both groups stratified for age groups,BMI and duration of symptoms (*n=500)*

Age Groups		**Groups**		P-value
	Ovulation	**Group A**	**Group B**	
20-30 years				
	YES	69(61.1%)	98(75.4%)	
	NO	44(38.9%)	32(24.6%)	0.01
31-40 years				
	YES	85(62.0%)	98(81.7%)	
	NO	52(38.0%)	22(18.3%)	0.00
BMI				
Normal				
	YES	56(58.3%)	77(80.2%)	0.00
	NO			
Over weight				
	YES	46(55.4%)	58(74.4%)	0.012
	NO	37(44.6%)	20(25.6%)	
Obese				
	YES	52(73.2%)	61(80.3%)	
	NO	19(26.8%)	15(19.7%)	0.313
Duration of symptoms				
1-5 years	YES	72(63.2%)	96(78.7%)	0.008
	NO	42(36.8%)	26(21.3%)	
6-10 years				
	YES	61(62.2%)	64(72.7%)	0.009
	NO	37(37.8%)	24(27.3%)	
11-15 years				
	YES	21(55.3%)	36(90.0%)	0.001
	NO	17(44.7%)	4(10.0%)	

Discussion: Polycystic ovarian syndrome is characterized by a combination of symptoms that may include irregular menstrual periods, ovulation problems, excess androgen levels and polycystic ovaries.(1, 13) PCOS can lead to various complications if left untreated.(14) So the present study was conducted with the main aim to compare the frequency of ovulation with myo-inositol alone versus in combination with clomiphene citrate for management of females presenting with polycystic ovarian syndrome. In this study, ovulation rates were assessed at 4, 8, and 12 weeks. After 4 weeks, ovulation was achieved in 114 (22.8%) patients, increasing to 272 (54.4%) at 8 weeks, and 350 (70%) at 12 weeks. When comparing the two treatment groups, after 4 weeks, ovulation occurred in 39 (15.6%) patients treated with myo-inositol alone and in 75 (30%) patients treated with myoinositol plus clomiphene citrate. At 8 weeks, ovulation rates were 119 (47.6%) and 153 (61.2%) for myo-inositol alone and myo-inositol plus clomiphene citrate, respectively. After 12 weeks, ovulation rates increased to 154 (61.6%) for myoinositol alone and 196 (78.4%) for myo-inositol plus clomiphene citrate. The difference in ovulation rates between the two treatment groups was statistically significant ($p<0.05$), indicating a higher efficacy of the combination therapy compared to myo-inositol alone in inducing ovulation in patients with polycystic ovarian syndrome. Our findings align with those of another randomized trial, where 61.7% of females treated with myo-inositol alone experienced ovulation, while 72.2% of females treated with the combination of myo-inositol and clomiphene citrate had ovulation. This consistency across studies strengthens the evidence supporting the efficacy of the combination therapy in inducing ovulation compared to myo-inositol alone in women with polycystic ovarian syndrome. In research led by Zdravko Kamenov et al.(15), it was found that following myo-inositol treatment, ovulation occurred in 29 women (61.7%), while 18 (38.3%) showed resistance to the treatment. Of those who ovulated, 11 (37.9%) went on to achieve pregnancy. Conversely, among the 18 patients resistant to myo-inositol, 13 (72.2%) ovulated after receiving clomiphene treatment. Among these ovulatory women, 6 (42.6%) became pregnant. These results highlight the effectiveness of clomiphene citrate in stimulating ovulation in patients unresponsive to myo-inositol treatment alone, with a significant number experiencing pregnancy post-ovulation. In a study conducted by Gupta et al. in 2017, involving 500 college girls aged 17–24, the reported prevalence rate of polycystic ovarian syndrome (PCOS) was
8.2%.(16) In our study, the mean age of patients in the myo-inositol group was 30.92 ± 5.91 years, while in the myo-inositol plus clomiphene citrate group, it was 30.24 ± 5.85 years. In the present study ovulation rates were significantly higher in patients aged 20-30 years (75.4%) and 31-40 years (81.7%) treated with myo-inositol plus clomiphene citrate compared to those treated with myo-inositol alone (61.1% and 62% respectively), indicating the superior efficacy of combination therapy in inducing ovulation in polycystic ovarian syndrome management across both age groups. In our study, stratifying data by BMI revealed significant differences in ovulation rates between patients treated with myo-inositol alone and those treated with myo-inositol plus clomiphene citrate. In normal BMI patients, ovulation rates were 58.3% with myo-inositol alone and 80.2% with the combination therapy, while in overweight patients, rates were 55.4% and 74.4%, respectively. Among obese patients, ovulation rates were 73.2% with myo-inositol alone and 80.3% with the combination therapy, with no significant difference noted. Stratification by duration of symptoms also revealed significant differences in ovulation rates. In patients with symptoms lasting 1-5 years, ovulation rates were 63.2% with myo-inositol alone and 78.7% with the combination therapy. Similarly, in patients with symptoms lasting 6-10 years, rates were 62.2% and 72.7%, respectively. Among patients with symptoms lasting 11-15 years, ovulation rates were 55.3% with myoinositol alone and 90% with the combination therapy. These findings suggest that the combination of myo-inositol and clomiphene citrate may be more effective in inducing ovulation across different BMI and symptom duration categories compared to myo-inositol alone in the management of polycystic ovarian syndrome. Elevated BMI is a common feature of PCOS and can exacerbate symptoms such as irregular menstrual cycles, infertility, and insulin resistance.(17) Therefore, managing BMI and promoting a healthy weight is an important aspect of PCOS treatment and can help alleviate symptoms and reduce the risk of long-term complications.

Conclusion: Our study concluded that the combination of myo-inositol and clomiphene citrate was significantly more effective in inducing ovulation in females with PCOS, confirming our hypothesis. With this local evidence in hand, we plan to implement the results of this study in our local setting to enhance treatment outcomes and alleviate the burden on hospitals and gynecologists. By promoting early ovulation, we aim to facilitate conception and improve overall patient care in the management of PCOS. ‘

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