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A Prospective Comparative Study of Metformin and Pioglitazone in Polycystic Ovarian Syndrome: Highlighting the Role of the Clinical Pharmacist

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is a multifaceted disorder characterized by a diverse collection of symptoms that range from mild to severe disturbances in reproductive, endocrine, and metabolic functions.

Objectives: To compare the effectiveness of Metformin and Pioglitazone in managing polycystic ovarian syndrome.

Methodology: This randomized, comparative, and observational study was conducted at ESI Hospital, Indiranagar, Bangalore, Karnataka, India. A total of 150 women aged 18-36 years diagnosed with PCOS participated in the study, which lasted six months. The participants were divided into two groups:

Group A: Received Metformin (500 mg twice daily) and Group B: Received Pioglitazone (15 mg once daily). Each group initially consisted of 75 participants to account for possible dropouts. Key inclusion criteria were the presence of anovulation, hyperandrogenism, and polycystic ovaries.

Results: Out of the enrolled patients, 72 (96%) in Group A and 75 (100%) in Group B completed the study. Initially, all participants experienced irregular menstrual cycles. By the study's conclusion, Group A: 31 (43%) achieved regular menstrual cycles and Group B: 46 (61%) achieved regular menstrual cycles.

Conclusion: Pioglitazone proved to be a more effective treatment for PCOS compared to Metformin.

Keywords: Polycystic Ovarian Syndrome; Metformin; Pioglitazone; Anovulation; Hyperandrogenism

Abbreviations

PCOS: Polycystic Ovarian Syndrome; LH: Luteinizing Hormone; SHBG: Sex Hormone Binding Globulin.

Introduction

Polycystic ovarian syndrome (PCOS) is a complex endocrine disorder characterized by a diverse range of symptoms

that vary in severity, affecting reproductive, endocrine, and metabolic functions. It is one of the most prevalent endocrine disorders in women, impacting approximately 5–7% of women of reproductive age and accounting for 30–60% of anovulatory infertility cases [1,2]. The hallmark features of PCOS include anovulation, polycystic ovaries, hyperandrogenism, central obesity, and an elevated risk of cardiovascular complications. Insulin resistance is a significant contributor to the pathophysiology of PCOS, alongside dyslipidaemia and vascular as well as endothelial dysfunctions. Obesity often exacerbates these metabolic abnormalities, further increasing the risk of glucose intolerance, type 2 diabetes mellitus, hypertension, and cardiovascular diseases [3-9].

Research has underscored the pathogenic role of insulin in PCOS. At a central level, insulin disrupts Luteinizing Hormone (LH) regulation, promoting ovarian androgen production by enhancing the activity of cytochrome P450 C17. This disruption leads to impaired follicular development, contributing to the clinical manifestations of PCOS. Women with PCOS have been found to experience hospital admissions twice as often as their counterparts without the condition over a 15-year follow-up period, emphasizing the significant health burden associated with the disorder [10].

In addition to pharmacological interventions, lifestyle modifications play a crucial role in managing PCOS. These include adopting a healthy diet rich in fresh vegetables, fruits, and high-fiber grains, maintaining an optimal body weight, and engaging in regular physical activity. Avoiding smoking, alcohol, excessive caffeine, and high-fat foods also helps manage the condition. Regular health check-ups are essential for early detection and prevention of complications.

Emerging evidence highlights the role of stress management in PCOS treatment. Chronic stress can exacerbate hormonal imbalances, contributing to irregular menstrual cycles and other symptoms. Practices such as mindfulness, yoga, and cognitive-behavioural therapy can be beneficial. Additionally, adequate sleep and mental health support are vital as they directly impact hormonal regulation.

Recent advancements in PCOS research also emphasize the potential of personalized medicine. Genetic predisposition plays a role in PCOS, and identifying genetic markers could enable tailored treatment plans. Furthermore, the integration of insulin sensitizers like Metformin and Pioglitazone with non-pharmacological approaches offers a comprehensive strategy to address the multifaceted challenges of PCOS. By combining lifestyle interventions, pharmacological treatments, and emerging research insights, the management of PCOS can be significantly optimized, improving both short-term symptoms and long-term health outcomes [10].

Aim and Objectives

- To compare between Metformin and Pioglitazone in the treatment of polycystic ovarian syndrome.
- To summarize the relative efficacy of Metformin and Pioglitazone in PCOS patients with insulin resistance, anovulation and hyperandrogenism.

Methodology

Study Design

This study was a randomized comparative and observational study conducted in the ESI Hospital, Indiranagar, Bangalore, Karnataka, India.

Study Sample Size

A total of 150 PCOS patients were enrolled in the age group of 18-36 years.

Study Site

The study was conducted in ESI Hospital, Indiranagar, Bangalore, Karnataka, India.

Study Period

The Study period was conducted for a period of 6 months from Feb- July 2023.

Study Criteria

Inclusion Criteria: Female patients of age group 18-36 years with the symptoms of anovulation, hyperandrogenism and polycystic ovaries on treatment with Metformin and Pioglitazone were included in the study and who were willing to participate in the study were included.

Exclusion Criteria: Patient who are below the age of 18 years, who are not on treatment with Metformin or Pioglitazone and who are not willing to participate in the study are excluded. Also, the patients who are taking any medications like estrogen and progesterone are also excluded.

Tools used

Prism graph pad tool used to analyze the data.

Results

Table 1 indicates the demographic profile of Group A indicates that the majority of patients (65.28%) had a BMI between 25–29.9, with most participants aged between 22–26 years (34.72%). A significant proportion were married (79.17%), lived in urban areas (86.1%), and followed a mixed diet (75%).

S.No	Demographics	Number of Patients	Percentage (%)
1	**Age Group(in Years)**		
	18-22	22	30.55
	22-26	25	34.72
	26-32	14	19.44
	32-36	11	17.27
2	**Marital Status**		
	Unmarried	15	20.83
	Married	57	79.17
3	**BMI**		
	<18.5	0	0
	18.5-24.9	23	31.9
	25-29.9	47	65.28
	≥30	2	2.7
4	**Place of Living**		
	Rural	10	13.8
	Urban	62	86.1
5	**Diet**		
	Vegetarian	18	25
	Mixed	54	75

Table 1: Demographic details of the Group-A subjects.

S. No	Demographics	Number of Patients	Percentage (%)
1	**Age Group (in Years)**		
	18-22	20	26.66
	22-26	28	37.37
	26-32	18	24
	32-36	9	12
2	**Marital Status**		
	Unmarried	17	22.6
	Married	58	77.3
3	**BMI**		
	<18.5	2	2.66
	18.5-24.9	24	36
	25-29.9	44	58.66
	≥30	5	6.66
4	**Place of Living**		
	Rural	12	16
	Urban	63	84
5	**Diet**		
	Vegetarian	15	20
	Mixed	60	80

Table 2: Demographic details of the Group-B subjects.

Table 2 Indicates the demographic profile of Group B reveals that the largest age group was 22–26 years (37.37%), with the majority of patients having a BMI of 25–29.9 (58.66%). Most participants were married (77.3%), lived in urban areas (84%), and followed a mixed diet (80%).

Table 3 and Figure 1 Indicates The baseline values indicate significant differences between Group A and Group B across all variables (P<0.0001). Group B exhibited higher mean values for F-G grading, fasting insulin, post-glucose insulin, and LH/FSH ratio, while Group A showed higher levels of SHBG and testosterone, reflecting distinct metabolic and hormonal profiles between the groups.

S. No	Variables	Group- A	Group- B	P Values
1	F-G Grading	12.9 ± 4.8	14.8 ± 4.5	P<0.0001
2	Total Cholesterol (mg/dl)	177.6 ± 15.4	180 ± 12.6	
3	HDL-C (mg/dl)	39.21 ± 2.1	40.2 ± 2.8	
4	VLDL-C (mg/dl)	38.43 ± 2.7	35.7 ± 2.3	
5	Fasting Insulin (µU/ml)	45.6 ± 5.5	47.3 ± 5.8	
6	Post Glucose Insulin (µU/ml)	140 ± 2.5	140 ± 3.5	
7	Testosterone (nmol/L)	2.1 ± 0.25	1.9 ± 0.3	
8	SHBG (nmol/L)	48.3 ± 1.3	35.5 ± 2	
9	FAI	11.9 ± 3.5	13.0 ± 3.1	
10	LH (mlU/ml)	4.8 ± 2.6	6.5 ± 3.1	
11	FSH(mlU/ml)	9.4 ± 1.5	7.9 ± 0.9	
12	LH/FSH	0.67 ± 1.2	0.93 ± 1.3	

Table 3: Comparison of baseline values of Group-A and Group-B.

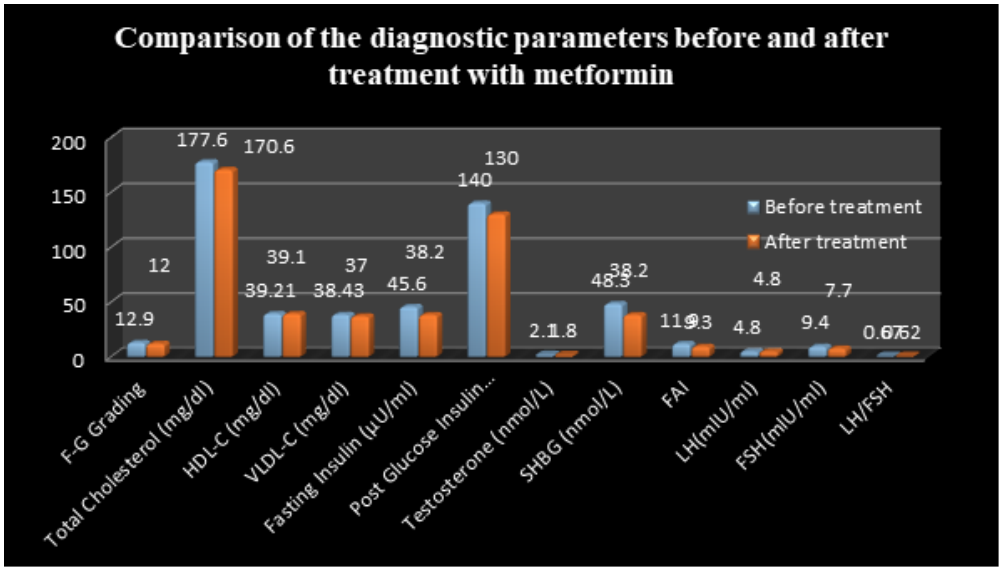

Figure 1: Comparison of baseline values of Group-A and Group-B.

Table 4 and Figure 2 Indicates the post-treatment values reveal significant improvements in both groups (P<0.0001). Group B showed greater reductions in F-G grading, total cholesterol, fasting insulin, and post-glucose insulin, along with higher increases in HDL-C and SHBG levels. These results highlight the superior metabolic and hormonal benefits of Pioglitazone compared to Metformin.

S. No	Variables	Group- A	Group- B	P Values
1	F-G Grading	12 ± 2.2	10.8 ± 2.4	P<0.0001
2	Total Cholesterol (mg/dl)	170.6 ± 10.4	160 ± 9.5	
3	HDL-C (mg/dl)	39.1 ± 2	60 ± 2.3	
4	VLDL-C (mg/dl)	37 ± 2.5	30.8 ± 2.5	
5	Fasting Insulin (µU/ml)	38.2 ± 3.7	28.2 ± 1.9	
6	Post Glucose Insulin (µU/ml)	130 ± 3	84.4 ± 3.6	
7	Testosterone (nmol/L)	1.8 ± 0.17	1.78 ± 0.25	
8	SHBG (nmol/L)	38.2 ± 1.5	70.5 ± 2.6	
9	FAI	9.3 ± 2.8	8.5 ± 1.5	
10	LH (mlU/ml)	4.8 ± 2.6	2.8 ± 1.2	
11	FSH (mlU/ml)	7.7 ± 1.5	7.5 ± 0.5	
12	LH/FSH	0.62 ± 1.07	0.37 ± 0.24	

Table 4: Post treatment values of group- A and group- B.

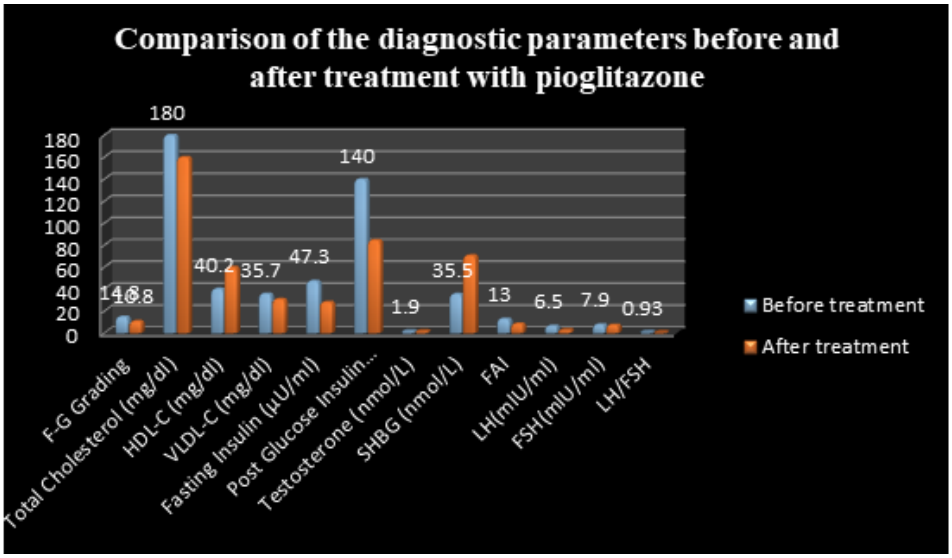

Figure 2: Post treatment values of group- A and group- B.

Discussion

The study was a randomized, comparative, and observational investigation comparing the efficacy of Metformin and Pioglitazone in treating polycystic ovarian syndrome (PCOS) alongside lifestyle modifications. Conducted in the Gynaecology department at ESI Hospital, Indiranagar, Bangalore, Karnataka, the research enrolled 150 female patients aged 18–36 years diagnosed with PCOS. Participants exhibited symptoms such as anovulation, hyperandrogenism, and polycystic ovaries. Patients under 18 years or not receiving Metformin or Pioglitazone were excluded.

The patients were divided into two groups:

- Group A: Received Metformin (500 mg twice daily).
- Group B: Received Pioglitazone (15 mg once daily).

The treatment duration was six months. At baseline, 42.17% of patients were normoinsulinemic, and 57.82% were hyperinsulinemic. However, the drug effects were not analysed in relation to varying insulin secretion levels. These findings differed from a comparative study by Sangeeta Shah, et al. [6], where 50% of patients achieved regular menstrual cycles, with 36% normoinsulinemic and 64%

hyperinsulinemia at baseline [11,12].

The study also observed changes in Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) levels [13,14], consistent with previous findings that PCOS prevalence is associated with alterations in these hormones, particularly when the LH/FSH ratio exceeds 2–3 [15,16]. A decrease in LH levels and the LH/FSH ratio was observed, especially in obese patients, aligning with prior research showing similar hormonal improvements predominantly in obese PCOS patients [17].

Regarding Ovulation Restoration

Group A: 30 out of 72 anovulatory patients (44.2%) achieved ovulation (CI 29–59%).
Group B: 38 out of 75 anovulatory patients (56%) achieved ovulation (CI 40.9–71.3%).
Pioglitazone demonstrated a higher success rate compared to Metformin, corroborating earlier studies but also differing slightly from findings that reported ovulation restoration rates of 44.2% and 56% for Metformin and Pioglitazone, respectively [18,19]. This reinforces Pioglitazone's effectiveness in improving PCOS symptoms [20].

Conclusion

The study concludes that Pioglitazone is more effective than Metformin in managing PCOS. It significantly restores menstrual cycles, achieves a higher ovulatory rate, and improves signs and symptoms of hyperandrogenism. Pioglitazone also demonstrates superior efficacy in enhancing insulin sensitivity in both obese and lean patients, potentially delaying or preventing the onset of type 2 diabetes mellitus more effectively than Metformin. Additionally, Pioglitazone shows notable improvements in lipid profiles, particularly by increasing HDL-C and reducing VLDL-C levels, thereby reducing cardiovascular risk. It also results in better hormonal balance, as evidenced by significant changes in LH/FSH ratios and SHBG levels, highlighting its comprehensive benefits in managing metabolic and endocrine disruptions in PCOS.

Role of Clinical Pharmacist in PCOD

Polycystic Ovarian Disorder (PCOD): PCOS is a common endocrine disorder in women, and its management often involves pharmacological interventions.
Medication management: Clinical Pharmacists assist health care providers in choosing appropriate medications for PCOS management.

- Dosing and administration, Monitoring and adverse effects, Medication adherence, Lifestyle modifications, Management of Insulin resistance, Patient education.
- Monitoring and Follow-up, Collaboration with health care team, Counselling and support, Management of coexisting conditions, Research and education.
- Clinical pharmacists are the valuable team of health care profession in managing PCOS.
- Their expertise in medication management, patient education and adherence support can contribute to improve outcomes and the overall well-being of individuals with PCOS.

Conflicts of Interest

Nil

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