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Efficacy of METFORMIN Alone versus Its Combination with SIMVASTATIN in the Management of Polycystic Ovary

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aims: To compare the effectiveness of treatment with METFORMIN alone and with a combination of METFORMIN and SIMVASTATIN in the management of polycystic ovarian syndrome.
Study Design: Randomized Clinical Trial.
Place and Duration of Study: Department of Obstetrics and Gynecology (Infertility Unit) at District Headquarter (DHQ) Teaching Hospital, Sahiwal (Pakistan) during June to September, 2018.
Methodology: 162 patients were randomly divided into METFORMIN group (n=81) and METFORMIN plus SIMVASTATIN group (n=81), detailed clinical history, including menstrual details, was taken with thorough examination performed. Baseline ultrasound was performed to evaluate the ovarian size and these were considered enlarged with volume >10cc or with >12

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follicles in any one ovary. Blood samples were taken at baseline and after three months of therapy to determine the LH/FSH ratio and lipid profile. Efficacy was defined as >15% decrease in the baseline values.

Results: The mean age of the patients was 27.12 ±8.17 years, and the mean BMI was 24.21 ±2.2 Kg/m^2. Efficacy was achieved in 67.1% patients with METFORMIN alone, while in 92.6% with combination medication (p=0.0068).

Conclusion: Managing the women having PCOS with the combination of METFORMIN and SIMVASTATIN is more beneficial as compared to treatment with METFORMIN alone.

Keywords: Polycystic ovarian syndrome; PCOS; METFORMIN; SIMVASTATIN.

ABBREVIATIONS

DHQ : District Headquarters
FSH : Follicle Stimulating Hormone
g/dL : gram per deci-litre
LH : Luteinizing Hormone
PCO : Polycystic Ovary (Ovarian)
PCOS : Polycystic Ovarian Syndrome
SD : Standard Deviation
SPSS : Statistical Package for Social Sciences

1. INTRODUCTION

Polycystic ovarian syndrome (PCOS) is common in about 10% of females of reproductive age group [1] and is the most common condition seen by the gynecologists. PCOS is related to hyper-androgenism, ovulatory dysfunction, and Polycystic Ovary (PCO) morphologically [2]. Other common associations of PCOS are obesity, menstrual irregularity, insulin resistance, and infertility. The patients are at an increased risk of abnormal lipo- proteins, hypertension, and cardio- and cerebrovascular morbidities [3,4].

The specific causative agents of PCOS are not clear and heterogeneous nature of syndrome is observed. It seems that it is developed due to the accumulation of different diseases sharing several pathophysiological characteristics [5]. Treatment of a patient with PCOS includes lifestyle modifications and pharmaceutical interventions, like oral contraceptives, antiandrogen therapy and blood glucose lowering medicines which in turn lead to decreased stimulation of insulin producing cells, hence lowering the levels of insulin and other androgenic hormones. METFORMIN is usually prescribed in females with PCOS. The resolution of PCOS with METFORMIN can be stimulated further with the addition of medicine, like SIMVASTATIN, which also decreases the ratio of Luteinizing Hormone (LH) to Follicle Stimulating Hormone (FSH) or what we call LH/FSH ratio. Therapy with METFORMIN and SIMVASTATIN is already in use for the aforementioned conditions [6,7].

METFORMIN is a biguanide which decreases insulin resistance and increases chances of ovulation and pregnancy, followed by declined insulin and androgen levels. SIMVASTATIN is a 3-hydroxy-3-methyl glutaryl co-enzyme A reductase inhibitor. It restricts the cholesterol bio-synthesis. SIMVASTATIN has antioxidant, anti-inflammatory and anti-androgenic properties. It inhibits the proliferation and steroidogenesis of the ovarian theca interstitial cells [6]. Some clinical trials so far have evaluated the effects of the combination of SIMVASTATIN and METFORMIN with monotherapy of METFORMIN only.

Keeping in view the paucity of ample evidence on these two agents and their role in the management of women with PCOS, the objective of this study was to compare the efficacy of METFORMIN alone versus METFORMIN plus SIMVASTATIN in the management of women with polycystic ovarian syndrome.

2. METHODOLOGY

A randomised clinical trial was carried out, during June 2018 to September 2018, in the Department of Obstetrics and Gynecology (Infertility Unit) at District Headquarter (DHQ) Teaching Hospital, Sahiwal which is a district level tertiary care healthcare facility in Pakistan. Approval from the ethical committee of the hospital was followed by inclusion of patients who presented during June and July 2018 based on the following criteria:

2.1 Inclusion Criterion

- Female patients of reproductive age group (18-45 years).

- Patients presenting Polycystic ovarian (PCO) endocrinopathy and having any two of the following;

  - Signs of hyperandrogenism
  - Ovulatory dysfunction / Menstrual abnormalities and irregularities
  - PCO morphology confirmed on Ultrasonography (USG)

2.2 Exclusion Criteria

- Patients who were having any other endocrine abnormality or patients with any chromosomal anomaly (e.g. Turner Syndrome)
- Patients with any form of liver or kidney disease.
- Patients who were taking any kind of exogenous hormones.
- Patients who were on any form of pharmacologic contraception.
- Patients who didn't consent to inclusion in the study.

A sum of 162 patients were selected for the sake of this study after calculation of sample size in the population of Sahiwal District (Sahiwal District has 381,468 females of reproductive age) using WHO sample size calculator for Bio Medical research and studies by taking 95% confidence level with 5% margin of error and considering the expected decrease in total cholesterol levels with METFORMIN alone to be 4.2%, and expected decrease in total cholesterol levels with SIMVASTATIN and METFORMIN to be 29.5%. Patients were further divided into two groups by systematic random sampling technique. Group-A (n=81) was the control group and was treated with METFORMIN alone while Group-B (n=81) was the interventional group and was given SIMVASTATIN in addition to METFORMIN.

Informed consent was taken from the patients fulfilling the inclusion criteria. The study patients were selected from both the in-patient and the out-patient departments of the study center. Detailed clinical history, including menstrual details, was taken along with thorough clinical examination performed. Baseline ultrasound was performed to evaluate ovarian size which were considered enlarged with volume more than 10 cc or with more than 12 follicular cysts (size of 2-9 mm) in any one ovary. A baseline intravenous blood sample was taken, by using a 5cc syringe and stored in sterile vials to determine the LH/FSH ratio and lipid profile. These were done at Department of Pathology, Sahiwal Medical College, Sahiwal.

LH and FSH levels were determined on Cobas 411 by electro chemiluminescence and lipid profile was done on Hitachi 902.The reports were verified by in-house hematologist. The patients in group-A were treated with oral METFORMIN (500 mg thrice daily) while patients in group-B received oral METFORMIN (500mg thrice daily) plus SIMVASTATIN (20 mg once daily at night). Then patients were followed up in OPD for 3 months with continuation of trial therapy. After three months, blood sample was again obtained to determine the LH/FSH ratio and lipid profile. Reports were assessed and efficacy was labelled, if there was >15% decrease in levels of lipid profile and LH/FSH ratio.

All information was gathered on a specifically designed Performa and Version 21 of the software Statistical Package for Social Sciences (SPSS) was used to analyse all this data. Efficacy, being a nominal data, was analysed as frequency along with percentage and was subjected to Chi-square test. While the quantitative data like age, baseline cholesterol, LH/FSH ratio, and BMI was represented as mean along with its standard deviation. P value below 0.05 was considered significant statistically, for the purpose of this study.

3. RESULTS

The mean age of the patients was 27.12 ±8.17 years. In this study, the mean BMI was 24.21 ±2.2 Kg/m^2. The mean LH/FSH ratio at baseline of the patients was 3.54 ±1.21. The mean LH/FSH ratio at the third month of the patients was 2.24 ±1.08. The mean total cholesterol value at baseline was 251.84 ±36.20 mg/dL. The mean total cholesterol value at the third month was 163.83 ±12.62 mg/dL.

Efficacy was achieved in 129 patients, out of whom 54 belonged to group A and 75 were from group B. Efficacy in patients having LH/FSH ratio below 3 at baseline was achieved in 61 cases; in which, 24 were from group A and 37 were from group B (Table 1). Similarly, the efficacy in patients having LH/FSH ratio above 3 at baseline was achieved in 68 cases, in which 30 were from group A and 38 were from group B. Statistically, a significant difference was found between the study groups and efficacy in patients having LH/FSH ration below 3, i.e. p=0.039.

Table 1. Comparison of efficacy in both the groups stratified based upon LH/FSH ratio

LH/FSH at baseline efficacy (Yes / No)	Group A (METFORMIN only Group)	Group B (Interventional Group)	P-Value*
≤3			
Yes	24	37	0.039
No	22	06	
≥3			
Yes	30	38	0.08
No	05	0	

**Pearson Chi-Square test*

Table 2. Comparison of efficacy in both the groups stratified by total cholesterol level

Total cholesterol efficacy (Yes / No)	Group A (METFORMIN only Group)	Group B (Interventional Group)	P-Value*
≤220 mg/dL			
Yes	29	26	0.061
No	10	01	
≥220 mg/dL			
Yes	23	52	
No	19	02	0.042

**Pearson Chi-Square test*

Table 2 shows that efficacy was achieved in 55 patients having less than 220 mg/dL total cholesterol value at baseline, among whom 29 were from group A and 26 were from group B. Efficacy was achieved in 75 patients having above 220 mg/dL total cholesterol value at baseline, out of whom 23 were from group A and 52 were from group B. Statistically, there was significant difference found between the study groups and efficacy in patients having total cholesterol value above 220 mg/dL, i.e. p=0.042. Overall efficacy was achieved in 79.6% cases. In Group A the efficacy was 67.1% while 92.6% efficacy was observed in Group-B where patients were given combination treatment (p=0.0068).

Data was also stratified for age. In age <30 years, efficacy was achieved in 30 (61.8%) with METFORMIN, while in 39 (92.9%) with combination. In age >30 years, efficacy was achieved in 22 (75%) with METFORMIN, while in 37 (92.3%) with combination.

4. DISCUSSION

PCOS is a complex disorder. It is described as raised androgen levels, irregular menstrual cycle, or cysts of small size in one or both side ovaries [8]. It affects at least 7% of females of reproductive age group [9]. According to National Institute of Health, the syndrome develops in about five million females capable of reproduction. About 5-10% females aged 18-44 years develop PCOS. Thus it becomes the most common endocrine anomaly in females of reproductive age group [10].

In this study, desired efficacy was achieved in 129 (79.63%) cases. Efficacy was 67.1% among the patients treated with METFORMIN alone while 92.6% where combination of METFORMIN and SIMVASTATIN was administered. There was significant difference between both groups. Not much data was published on this topic in literature. However, some of the previous studies are discussed below.

Banaszewska et al. included 113 subjects in their study. With SIMVASTATIN alone, androgenic hormones reduced significantly. But LH or FSH did not decrease either with SIMVASTATIN or METFORMIN alone or in combination. Total cholesterol and low-density lipoprotein also reduced significantly with SIMVASTATIN and combination of SIMVASTATIN and METFORMIN. The number of menstruations increased and ovarian volume decreased more in patients taking SIMVASTATIN. They concluded that SIMVASTATIN has better outcome than METFORMIN, but the combination of SIMVASTATIN and METFORMIN and SIMVASTATIN alone almost had equal results [6].

Experimental trials showed that METFORMIN can help in reduction of androgen levels

significantly, increase insulin sensitivity and stimulate weight loss in females having PCOS. One trial proposed that METFORMIN, if used during pregnancy, has nine times reduction in risk of gestational diabetes in pregnant females with PCOS. As well as, along with prevention from gestational diabetes in pregnant females having PCOS, METFORMIN can also decrease the chance of preeclampsia in these females [11]. Gestational diabetes and preeclampsia usually develop due to deranged levels of lipid profile. So, SIMVASTATIN can help in controlling lipid levels and preventing derangement of these levels and thus improves the chances of conception and reduces the risk of gestational diabetes mellitus and preeclampsia.

A longitudinal study proposed that METFORMIN can also help boost up the metabolic system of females with PCOS, if given as 36 months treatment; especially it improves high-density lipoprotein in blood, diastolic blood pressure and BMI. But insufficient data is available, which could recommend the prescription of METFORMIN to all females having PCOS [12].

On flip side of the coin, the study conducted by Carrick demonstrated that the SIMVASTATIN therapy for patients with PCOS appears to possibly result in significant decreases in testosterone levels, and therefore reduce the clinical signs of PCOS. However, SIMVASTATIN plus METFORMIN therapy does not provide much, if any, additional reduction in metabolic parameters [13].

A study by Kazerooni et al. revealed that combination of SIMVASTATIN and METFORMIN decreased total cholesterol more than 15% from baseline by 29.5% versus 4.2% with METFORMIN and placebo after 3 months of therapy. LH/FSH ratio significantly decreased by 38.3% and increased by 4.4% after 3 months of therapy with METFORMIN plus SIMVASTATIN and METFORMIN plus placebo, respectively [1]. Other meta-analysis and systematic reviews proposed that in females with PCOS having a particular category, METFORMIN can help improve reproductive function regardless of insulin resistance and glucose intolerance [14]. METFORMIN can also help in reducing significantly liver fat indicators in obese females having PCOS [15].

There is deficiency of evidence regarding the efficacy of SIMVASTATIN and METFORMIN combination therapy for PCOS. Larger trials are needed for prolonged period and large sample size to get more evidence regarding beneficial aspects of combination of SIMVASTATIN plus METFORMIN and also side effects, if any.

5. CONCLUSION

The combination of METFORMIN plus SIMVASTATIN group showed more efficacious results as compared to METFORMIN alone in the treatment of polycystic ovarian syndrome patients. So the combination of METFORMIN plus SIMVASTATIN is a better choice for treatment of PCOS in comparison with METFORMIN alone but a lot more research is needed to explore this topic further.

CONSENT

Informed consent was taken from the patients fulfilling the inclusion criteria.

ETHICAL APPROVAL

Approval from the ethical committee of the hospital was taken by the author.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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