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Original Research Article

Effect of metformin in treating polycystic ovarian syndrome among women attending a tertiary care setting -A prospective observational study

Suresh Chandra Mondal[1,*], Pinaki Sarkar[2]

[1]*Dept. of Obstetrics & Gynaecology, Malda Medical College & Hospital, Malda, West Bengal, India*
[2]*Balurghat Nursing Home, Balurghat, West Bengal, India*

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ABSTRACT

Aim: To determine the efficacy of metformin on clinical profile and metabolic disorders in women with polycystic ovarian syndrome. Polycystic ovarian syndrome, is a heterogeneous endocrinological disorder affecting women of reproductive age and metformin was introduced to influence the pathogenesis.

Materials and Methods: A prospective observational study was conducted on 100 women with polycystic ovarian syndrome, attending department of gynaecology in a tertiary care setting and were divided into two group of 50 each. Metformin was used in 50 patients for one year. Rest 50 patients were advised about diet control and exercise. The parameters like body mass index (BMI), weight, hormonal imbalance, ovulation, and menstrual changes were analysed in both groups. Descriptive statistics for mean, SD were carried and chi-square test was used to test statistical significance using coGuide version V.1.0 and p value set at < 0.05.

Results: The mean age was 25±10 years. Both the groups were comparable with respect to BMI and weight. There was a significant difference between the groups with respect to fasting insulin, which reduced to 7.44±1.12 from 11.97±2 mIU/ml, testosterone levels reduced to 0.59±0.1 from 0.76±0.3 mIU/ml, luteinizing hormone levels reduced to 8.55±2 from 20.01±7.3 mIU/ml, and LH:FSH ratio reduced to 1.11±0.1 from 2.31±0.2 mIU/ml. In the metformin group, 22 (44%) participants were anovulation before treatment, and ovulation started in 15 (30%) after treatment which was not seen other group.

Conclusion: Clinical, hormonal, and biochemical changes in polycystic ovarian syndrome may effectively be treated by metformin.

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1. Introduction

Polycystic ovary syndrome (PCOS) affects women of reproductive age. It is a complex endocrine condition with a prevalence of 15%–20%.[1] The presence of any two of three features; hyperandrogenism (clinical or biochemical), ovulatory dysfunction (often manifested by menstrual irregularities), and polycystic ovarian morphology (PCOM) by ultrasound is defined as PCOS by the Rotterdam Consensus which is jointly held by the European and the North American Associations of Reproductive Medicine in 2003.[2] Rotterdam criteria is used in adults for PCOS diagnosis as recommended by a recent guideline from the International PCOS Network.[3]

PCOS is characterized by biochemical and clinical features of excess androgen levels (hirsutism and acne), menstrual irregularities, and polycystic morphology of the ovaries.[4] A high prevalence of impaired glucose tolerance and insulin resistance, which are drivers of type 2 diabetes mellitus (T2DM), is commonly seen in women with PCOS.[5] About 40%-50% prevalence of the metabolic syndrome is seen in women with PCOS, compared with the general population.[6] Infertility, increased body weight, endometrial cancer, and an increased risk of cardiovascular disease (CVD) are another spectrum of complications associated with PCOS.[7,8]

* *Corresponding author*.
E-mail address: sureshmondal77@gmail.com (S. C. Mondal).

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The literature on lifestyle intervention in preventing PCOS is mainly disappointing,[9] and hence preventing and managing metabolic comorbidities in PCOS by using pharmacotherapy is the cornerstone; yet the effect of pharmacotherapy agents in treating PCOS is unexplored as they are used primarily to treat other conditions. A member of the biguanide family, metformin is with proven safety and efficacy. Previous studies by Seli et al.[10] in 2002 and Kazerooni et al.[11] in 2003 reported incompatible results on the effects of metformin therapy on hyperandrogenism in women with polycystic ovarian syndrome. Restoring ovulation, reducing weight, reducing circulating androgen levels, reducing the risk of miscarriage, and reducing the risk of gestational diabetes mellitus are some of the good deal of effects of metformin in PCOS. Metformin is also used in treating type 2 diabetes for a long time and is one of the insulin-sensitizing agents commonly used in the treatment of PCOS,[12] though it is still an unlicensed indication in PCOS.

With this background, the present study is aimed to provide the efficacy of metformin on clinical profile and metabolic disorders in women with PCOS attending a tertiary care setting.

2. Materials and Methods

2.1. Study design

Prospective observational study.

2.2. Source population

Women with PCOS attending the outpatient department (OPD) of gynaecology and endocrinology department of tertiary care setting.

2.3. Study population

Women with PCOS**.**

2.4. Sample size

A total of 100 subjects were selected based on convenience and divided into two groups of 50, each based on inclusion criteria. Group A received metformin and group B received advice on lifestyle and diet modification.

2.5. Sampling technique

For the feasibility of the study, convenience sampling was used.

2.6. Ethical and informed consent

Ethical permission was obtained from the ethical committee review board of the concerned hospital, and written informed consent was obtained from subjects before the start of the study. Confidentiality of the subjects was maintained.

2.7. Study period

From 1st February 2019 to 31st January 2020.

2.8. Inclusion criteria

1. PCOS by Rotterdam criteria
2. BMI >25
3. Normal glucose levels

2.9. Exclusion criteria

1. BMI <25
2. Type 2 diabetes
3. Treatment with other drugs
4. Pregnant women
5. History of bariatric surgery

2.10. Data collection

We identified 100 patients diagnosed with PCOS referred to the first endocrine check-up during the selected time period. The patients were recruited after the diagnosis of PCOS based on the Rotterdam criteria, which was confirmed by reviewing the medical records. Each patient's age biochemical features like increased LH/FASH ratio, increased insulin, increased testosterone, TSH, prolactin, fasting glucose; insulin < 4.5:1; ultrasonic findings of multiple (>10), small (2-8 mm) peripheral cysts (> 8 ml) ovaries to diagnose polycystic ovaries. All the hormones were measured by the ELISA method.

2.11. Intervention

Fifty cases were treated with metformin (1500 mg/day) for one year. Other 50 cases were given lifestyle and diet modifications. All patients were counselled regarding lifestyle changes at every visit as a routine part of clinical care. Alteration in weight, BMI, menstrual cycles, ovulatory response, and hormonal changes were critically analysed. Those tests were repeated every three months to watch the response. These results were compared with the rest 50 patients of the same weight and BMI range who did not receive metformin.

2.12. Statistical analysis

Menstrual disorder, hirsutism, acne, and ovulation were considered as primary outcome variables. The study group (group A and group B) was considered as a primary explanatory variable. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency, and proportion for categorical variables. The association between categorical explanatory variables and

the quantitative outcome was assessed by comparing the mean values. To assess the statistical significance of normally distributed variables independent samples t-test was used. The association between the study group and categorical outcomes was assessed by cross tabulation and comparison of percentages. The chi-square test was used to test statistical significance. The p value of < 0.05 was considered significant. The coGuide version V.1.0 was used for statistical analysis.[13]

3. Results

All 100 participants were included in the final analysis, where 50 were in group A (metformin), and 50 were in group B (exercise and diet modification). The mean age was 25±10. Among the study population, 5 (10%) participants had amenorrhea in group A, and 4 (8%) participants had amenorrhea in group B, 22 (44%) participants had oligomenorrhea in group A, and 4 (8%) participants had oligomenorrhea in group B, 16 (32%) participants had hypomenorrhea in group A, and 24 (48%) participants had hypomenorrhea in group B. There was no statistically significant difference in the proportion of all menstrual disorder between the study group (P Value>0.05). (Table 1)

No significant difference was noted in mean BMI and weight before and after treatment between the study group (p Value>0.05), while there was a significant mean difference for parameters like fasting insulin, testosterone, LH, and LH: FSH (p Value<0.05). (Table 2)

A significant difference was not seen, in the proportion of hirsutism and acne, before and after treatment between the study group (p Value>0.05). (Table 3)

No statistically significant difference was seen in the proportion of ovulation, before and after treatment, between the study group (p Value>0.05) but the proportion reduced to 15 (30%) in the metformin group. (Table 4)

4. Discussion

The findings of the present study showed the efficacy of metformin in treating PCOS. A statistically significant difference was seen after one year of treatment with metformin in the study group with respect to reduction in BMI to ≥25 kg/m2, normal baseline glucose levels, increased menstrual regularity, and improved androgen profile. In the majority of women that subsequently remained on therapy, and overall beneficial steady state was observed at three months follow up.

4.1. Impact on body weight

In the present study, there was no significant difference in mean BMI and weight before and after treatment between study groups (p value>0.05), which is in contrast to a study done by J. Mojca et al.[12] by where mean BMI decreased for 3.7% after the first year and remained stable up to four years of follow-up. A meta-analysis on 630 participants with PCOS, who were treated with metformin for six months reported no evidence of its effect on BMI.[14]

4.2. Impact on menstrual regularity

Metformin uses in PCOS is not consistently associated with improvements in menstrual regularity. In a Cochrane review that included a meta-analysis of 38 RCTs of 3495 women with PCOS, metformin therapy only marginally improved menstrual patterns.[14] In our study, the menstrual disorder was decreased in 31 (62%) of group A subjects, which were high when compared to group B. This finding was in comparison to J Mojca et al.[12] where menstrual frequency increased after the first year and normalized in the majority of patients in the following years. Increased menstrual frequency correlated with the decrease in total testosterone in LH, FSH, and insulin, which is in contrast to j Mojica et al,[12] where there was no correlation seen in LH/FSH. All these disturbances are established determinants of menstrual regularity.[15]

4.3. Impact on androgens

Testosterone levels reduced by 20%–25% in women who were using metformin for PCOS.[16] In comparison with the women in whom androgens remained unchanged or increased, women in whom androgens decreased had the worst androgen profile at baseline. It is considered that metformin reduces testosterone levels by lowering hyperinsulinemia.[5,17] There was a decrease in levels of testosterone in the present study.

Hirsutism and acne: There was no subsequent decrease in hirsutism and acne in both the study groups, which was not statistically significant. This finding contrasts to a study where combination therapy demonstrated substantial reductions in free testosterone, androstenedione, and LH levels with an approximately 30% decrease in the hirsutism score.[18]

4.4. Impact on metabolic features

Diabetes: Irrespective of age and BMI, women with PCOS are at an increased risk of type 2 diabetes as reported by the most recent Australian Longitudinal Study on Women's Health database.[2] This variable was not recorded in the present study.

Ovulation: In the present study, 15 (30%) subjects of group A and 9 (18%) showed improvement in ovulation. The majority was with group A. An interesting case report has shown the efficacy of metformin in an underweight young PCOS patient with oligomenorrhea and hirsutism.[19]

Higher metformin doses have been beneficial, but metformin intolerance and its associated adverse events were not considered in the present study. Evidence also suggests of developing vitamin B12 deficiency with

Table 1: Comparison of alterations in menstrual disorder after treatment with metformin between study group (N=100)

Menstrual disorder	Study Group		P Value
	Group A (N=50)	Group B (N=50)	
Amenorrhea	5 (10%)	4 (8%)	0.505
Cycle restored	3 (6%)	1 (2%)	
Oligomenorrhea	22 (44%)	18 (36%)	0.064
Cycle restored	18 (36%)	5 (10%)	
Hypomenorrhea	16 (32%)	24 (48%)	0.270
Cycle restored	10 (20%)	8 (16%)	

Table 2: Comparison of changes in parameters before and after treatment between the study group (N=100)

Parameters	Study Group		P Value
	Group A (N=50)	Group B (N=50)	
BMI (kg/m ^{2})			
Before treatment	24.07±5	23.33±4	0.42
After treatment	22.88±3	23.00±4	0.87
Weight (kg)			
Before treatment	54.02±8.2	53.95±7.1	0.96
After treatment	51.52±5.8	52.76±6	0.29
Fasting insulin [mIu/ml]			
Before treatment	11.97±2	10.74±1.7	0.001
After treatment	7.44±1.12	10.95±2	<0.001
Testosterone			
Before treatment	0.76±0.3	0.66±0.1	0.03
After treatment	0.59±0.1	0.69±0.22	0.004
LH [mIu/ml]			
Before treatment	20.01±7.3	13.86±4.5	<0.001
After treatment	8.55±2	13.01±5	<0.001
LH: FSH			
Before treatment	2.31	2.11	<0.001
After treatment	1.11	2.09	<0.001

Table 3: Comparison of hirsutism and acne before and after treatment between the study group (N=100)

Parameters	Study Group		P Value
	Group A (N=50)	Group B (N=50)	
Hirsutism			
Before treatment	32 (64%)	28 (56%)	1.000
After treatment	32 (64%)	28 (56%)	
Acne			
Before treatment	16 (32%)	18 (36%)	0.895
After treatment	15 (30%)	18 (36%)	

Table 4: Comparison of the effect of metformin on ovulation before and after treatment between study groups

Parameters	Study Group		P Value
	Group A (N=50)	Group B (N=50)	
Oligo/ anovulation (Before treatment)	22 (44%)	20 (40%)	0.425
Ovulation (After treatment)	15 (30%)	9 (18%)	

prolonged use of metformin.[20]

The major strength of the present study is the prospective study design where the patients were followed to evaluate the efficacy of metformin in treating PCOS in a real-life setting. Clinical homogeneity was achieved by reviewing the medical records of all 100 patients that had been referred to our clinics from 2016 to 2018.

5. Limitation

The sample size was relatively small, and it was a single-center study. As the study was observational and as there was no randomization of patients, the number of patients in each arm of treatment could not be controlled. Adherence to medication and lifestyle modifications were not evaluated in the present study, and hence a causal effect on the use of metformin combined with lifestyle modifications in improving the symptoms of PCOS in women cannot be generated. Regardless of the shortcomings, the data collected in the present study suggest that metformin treatment combined with lifestyle modifications improves the well-being of patients with PCOS. Other comorbidities were also not included in the study, which can act as confounders. We recommend conducting multi-centric randomized controlled trials including other comorbidities on a large sample to verify the findings of this study.

6. Conclusion

Marked reduction in LH and insulin by metformin in our cases was a very significant observation. Metformin produces minimal changes in hirsutism and has the potential to alter the function of ovulation-inducing drugs.

7. Source of Funding

The project was self-funded. No external agency had funded the project.

8. Conflict of Interests

The authors declare no conflicts of interest.

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Author biography

Suresh Chandra Mondal, Assistant Professor

Pinaki Sarkar, Residential Medical Officer

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