International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2022; 6(1): 107-110
Received: 24-11-2021
Accepted: 26-12-2021

Dr. Jayshriben Rajeshkumar Majithiya
Assistant Professor, Department of Obstetrics & Gynecology, Banas Medical College and Research Institute, Palanpur, Gujarat, India

Dr. Rajeshkumar Hiralal Majithiya
Assistant Professor, Department of Surgery, Banas medical college and research institute, Palanpur, Gujarat, India

Corresponding Author:
Dr. Jayshriben Rajeshkumar Majithiya
Assistant Professor, Department of Obstetrics & Gynecology, Banas Medical College and Research Institute, Palanpur, Gujarat, India

Efficacy of metformin in treating polycystic ovarian syndrome among women: A observational study

Dr. Jayshriben Rajeshkumar Majithiya and Dr. Rajeshkumar Hiralal Majithiya

DOI: https://doi.org/10.33545/gynae.2022.v6.i1b.1122

Abstract
Background and Aim: 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 Polycystic ovary syndrome (PCOS). 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.
Material and Methods: Present Observational study was conducted in Women with PCOS attending the outpatient department (OPD) of Gynaecology and endocrinology department of tertiary care setting. A total of 160 subjects were selected based on convenience and divided into two groups of 80, each based on inclusion criteria. Group A received metformin and group B received advice on lifestyle and diet modification. 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.
Results: 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 Value0.05). 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 in the metformin group.
Conclusion: Compared with control interventions, metformin appears to be an effective intervention for overweight women with PCOS. 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.

Keywords: Body mass index, insulin, metformin, polycystic ovary syndrome

Introduction
Polycystic ovary syndrome (PCOS) is a common gynaecological endocrine disease in women of childbearing age [1]. PCOS is characterized by excessive androgens, persistent anovulation, infertility, and metabolic disorders [2]. The morbidity rate is 6% to 15% among women during the childbearing period, and to date, the cause is not completely clear. Extensive clinical and epidemiological data show that approximately 50% of PCOS patients are overweight or obese [3]. Overweight women with PCOS suffer more severe endocrine and metabolic disorders than nonoverweight patients [4].
PCOS is characterized by biochemical and clinical features of excess androgen levels (hirsutism and acne), menstrual irregularities, and polycystic morphology of the ovaries. 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].
In addition to impaired insulin responsiveness of adipocytes, being overweight may also cause lipodystrophy and insulin resistance by reducing the expression of lipid droplet proteins in adipocytes [9, 10]. Karimi *et al.* [11] and Heshmati *et al.* [12] suggest that patients with polycystic ovary syndrome generally have insulin resistance and elevated serum insulin and abnormal lipoprotein metabolism.

The literature on lifestyle intervention in preventing PCOS is mainly disappointing 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 [13]. 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, though it is still an unlicensed indication in PCOS.[14] 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.

Material and Methods

Present Observational study was conducted in Women with PCOS attending the outpatient department (OPD) of gynaecology and endocrinology department of tertiary care setting. A total of 160 subjects were selected based on convenience and divided into two groups of 80, each based on inclusion criteria. Group A received metformin and group B received advice on lifestyle and diet modification. Ethical approval was taken from the institutional ethical committee and written informed consent was taken from all the participants.

Inclusion criteria

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

Exclusion criteria

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

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.

Eighty cases were treated with metformin (1500 mg/day) for one year. Other 80 cases were given lifestyle and diet modifications. All patients were counseled 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 analyzed. Those tests were repeated every three months to watch the response. These results were compared with the rest 80 patients of the same weight and BMI range who did not receive metformin.

Statistical analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2007) and then exported to data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). For all tests, confidence level and level of significance were set at 95% and 5% respectively.

Results

All 160 participants were included in the final analysis, where 80 were in group A (metformin), and 80 were in group B (exercise and diet modification). The mean age was 26.40±10.32 Among the study population, 8 (10%) participants had amenorrhea in group A, and 7 (8.75%) participants had amenorrhea in group B, 35 (43.75%) participants had oligomenorrhea in group A, and 7 (8.75%) participants had oligomenorrhea in group B, 26 (32.5%) participants had hypomenorrhea in group A, and 38 (47.5%) 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). 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 Value0.05). (Table 1) 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 in the metformin group.

Table 1: Comparison of changes in parameters before and after treatment between the study group (N=160)

Variable	Group A	Group B	P value
BMI (kg/m^2)			
Before treatment	24.05±4	23.10±3	0.4
After treatment	22.65±2	23.04±5	0.5
Weight (kg)			
Before treatment	54.01±8.1	53.26±7.0	0.8
After treatment	51.40±5.7	52.50±5	0.7
Fasting insulin [mIu/ml]			
Before treatment	11.80±2	10.50±1.6	0.02*
After treatment	7.32±1.12	10.95±1	0.001*
Testosterone			
Before treatment	0.71±0.2	0.62±0.1	
After treatment	0.58±0.1	0.68±0.20	
LH [mIu/ml]			
Before treatment	20.12±7.3	13.70±4.4	
After treatment	8.47±2	13.09±5	
LH: FSH			
Before treatment	2.30	2.10	
After treatment	1.09	2.07	

Table 2: Comparison of hirsutism and acne before and after treatment between the study group (N=160)

Variable	Group A	Group B	P avleu
Hirsutism			
Before treatment	52 (65%)	44 (55%)	0.85
After treatment	52 (65%)	44 (55%)	
Acne			
Before treatment	26 (32.5%)	29 (36.25%)	0.26
After treatment	25 (31.5%)	29 (36.25%)	

Statistically significant at p≤0.05

Discussion

Polycystic ovary syndrome (polycystic ovary syndrome, PCOS) is a gynaecological endocrine disorder commonly seen in women of reproductive age and has highly heterogeneous clinical manifestations [15]. Approximately 70% of PCOS patients are overweight or obese, and PCOS may be related to genetic, environmental factors including diet, lifestyle, and hormone levels [16]. Obesity as a risk factor often causes female

diseases such as breast cancer [17]. Studies have found that, with increases in weight, abnormal genes such as the Wnt signaling pathway, oxidative stress, and inflammation in adipose tissue of PCOS patients are abnormal [18], suggesting that obesity participates in the pathogenesis of PCOS [19], triggers metabolic and reproductive disorders, and may also cause glycolipid metabolism, hyperandrogenaemia, menstrual disorders, infertility, and comorbidities related to polycystic ovary syndrome [20]. Furthermore, we also noticed that many features and complications of polycystic ovary syndrome (PCOS) can trigger oxidative stress and increase insulin resistance index [21, 22]. Obese women with PCOS show lower ISOGTT and higher LH to stimulate androgen secretion, triggering insulin resistance and excessive androgens [23].

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/m^2, normal baseline glucose levels, increased menstrual regularity, and improved androgen profile.

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.* [14] 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 [24].

Metformin uses in PCOS are 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 [24]. A large number of studies have shown that metformin can not only reduce weight and metabolic disorders but also correct menstrual patterns, restore ovulation, and even allow conception [25-26]. Furthermore, in previous systematic reviews, the specific therapeutic effect of metformin on metabolic indicators in overweight women with PCOS has not been evaluated. Through quantitative synthesis, we found that as a drug that regulates the metabolism of overweight women with PCOS, metformin seems to have a partial effect, can reduce BMI and WC, and can reduce testosterone, FSH, LH, and LDL cholesterol.

Testosterone levels reduced by 20%–25% in women who were using metformin for PCOS [47]. 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 [48]. There was a decrease in levels of testosterone in the present study. 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 [5, 6]. This variable was not recorded in the present study. Ovulation: In the present study 30% subjects of group A and 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 [49]. Our research results found that metformin has a lowering effect on FSH in overweight PCOS patients. It can be considered as abnormal gonadotrophic secretion in women with overweight PCOS, which makes FSH in an abnormal secretion stage [50]. The antireproductive effect of metformin helps correct this phenomenon [51]. The production of polycystic ovary syndrome is directly related to the abnormality of insulin. Insulin resistance will cause hyperinsulinemia, which directly affects the role of ovarian receptors, inhibits insulin binding protein and sex hormone-binding protein, while freeing testosterone and increasing ovarian androgens. Therefore, metformin is used to regulate insulin secretion and achieve the purpose of effectively improving polycystic ovary syndrome.

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.

Conclusion

Compared with control interventions, metformin appears to be an effective intervention for overweight women with PCOS. We have to admit that this study may have some serious limitations. Different treatment options, doses, duration, and enrolment of different populations may have led to obvious heterogeneity, and we need to interpret the results carefully. 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.

References

1. Legro RS, Arslanian SA, Ehrmann DA, *et al*., "Diagnosis and treatment of polycystic ovary syndrome: an endocrine society clinical practice guideline," 7e Journal of Clinical Endocrinology & Metabolism. 2013;98(12):4565-4592.
2. Norman RJ, Dewailly D, Legro RS, Hickey TE. "Polycystic ovary syndrome," 7e Lancet. 2007;370;9588:685-697.
3. Mu L, Zhao YR, Li Y, Lai, Qiao J. "Metabolic characteristics of normal weight central obesity phenotype polycystic ovary syndrome women: a large-scale national epidemiological survey," Reproductive Biomedicine Online. 2018;37(4):498-504.
4. Arya S, Hansen KR, Wild RA. "Metformin, rosiglitazone, or both for obese women with polycystic ovary syndrome?" Fertility and Sterility. 2020;113(1):87-88.
5. Salley KES, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. Glucose intolerance in polycystic ovary syndrome–a position statement of the Androgen Excess Society. J Clin Endocrinol Metab. 2007;92(12):4546-56. doi:10.1210/jc.2007-1549.
6. Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and Characteristics of the Metabolic Syndrome in Women with Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2005;90(4):1929-35. doi:10.1210/jc.2004-1045.
7. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis.Nat Rev Endocrinol. 2011;7(4):219-31.
8. Mu N, Zhu Y, Wang Y, Zhang H, Xue F. Insulin resistance: a significant risk factor of endometrial cancer. Gynecol Oncol. 2012;125(3):751-7.
9. Shi B, Feng D, Sagnelli M, *et al*., "Fructose levels are elevated in women with polycystic ovary syndrome with obesity and hyperinsulinemia," Human Reproduction. 2020;35:187-194.
10. Czech MP. "Insulin action and resistance in obesity and

type 2 diabetes," Nature Medicine. 2017;23(7):804-814.
11. Karimi E, Heshmati J, Shirzad N, *et al*., "effect of synbiotics supplementation on anthropometric indicators and lipid profiles in women with polycystic ovary syndrome: A randomized controlled trial," Lipids in Health and Disease. 2020;19:60.
12. Heshmati J, Farsi F, Yosaee S, *et al*., "-e effects of probiotics or synbiotics supplementation in women with polycystic ovarian syndrome: a systematic review and meta-analysis of randomized clinical trials," Probiotics and Antimicrobial Proteins. 2019;11(4):1236-1247.
13. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2011;(2):CD007506. doi:10.1002/14651858.cd007506.pub3.
14. Jensterle M, Kravos NA, Ferjan S, Goricar K, Dolzan V, Janez A. Long-term efficacy of metformin in obese PCOS: longitudinal follow up of retrospective cohort. Endocr Connect. 2019;9(1):44-54. doi:10.1530/ec-19-0449.
15. Neven J, Laven Teede H, Boyle J. "A summary on polycystic ovary syndrome: diagnostic criteria, prevalence, clinical manifestations, and management according to the latest international guidelines," Seminars in Reproductive Medicine. 2018;36(1):005-012.
16. Lim SS, Davies MJ, Norman RJ, Moran LJ. "Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and metaanalysis," Human Reproduction Update. 2012;18(6):618-637.
17. Namazi N, Irandoost P, Heshmati J, Larijani B, Azadbakht L. "-e association between fat mass and the risk of breast cancer: a systematic review and meta-analysis," Clinical Nutrition. 2019;38(4):1496-1503.
18. Chazenbalk GD, Phan JD, Madrigal V, Ding X, X. Li, Dumesic A. "Abnormal expression of genes governing adipogenesis and extracellular matrix (ecm) formation IN subcutaneous (SC) abdominal adipose stem cells (ASCS) OF lean polycystic ovary syndrome (PCOS) women," Fertility and Sterility. 2015;104(3):E20.
19. Tang L, Yuan L, Yang G, *et al*., "Changes in whole metabolites after exenatide treatment in overweight/obese polycystic ovary syndrome patients," Clinical Endocrinology. 2019;91(4):508-516.
20. Shaaban Z, Khoradmehr A, Amiri-Yekta A, Jafarzadeh Shirazi MR, Tamadon A. "Pathophysiologic mechanisms of obesity- and chronic inflammation-related genes in etiology of polycystic ovary syndrome," Iranian Journal of Basic Medical Sciences. 2019;22(12):1378-1386.
21. Heshmati J, Golab F, Morvaridzadeh M, *et al*., "-e effects of curcumin supplementation on oxidative stress, Sirtuin-1 and peroxisome proliferator activated receptor c coactivator 1α gene expression in polycystic ovarian syndrome (PCOS) patients: a randomized placebo-controlled clinical trial," Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14(2):77-82.
22. Heshmati J, Omani-Samani R, Vesali S, *et al*., "-e effects of supplementation with chromium on insulin resistance indices in women with polycystic ovarian syndrome: a systematic review and meta-analysis of randomized clinical trials," Hormone and Metabolic Research. 2018;50(3):193–200.
23. Diamanti-Kandarakis E, Dunaif A. "Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications," Endocrine Reviews 2012;33(6):981-1030.
24. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulinsensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiroinositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database Syst Rev. 2012;(5):CD003053. doi:10.1002/14651858.cd003053.pub5.vol. 358, no. 19, pp. 2003–2015, 2008.
25. Fraison E, Moran L, Bilal S, Ee C, Venetis C, Costello M. "Metformin versus the combined oral contraceptive pill for hirsutism, acne, and menstrual pattern in polycystic ovary syndrome," Human Reproduction. 2019;34(458):46.
26. Bordewijk EM, Nahuis M, Costello MF, *et al*., "Metformin during ovulation induction with gonadotrophins followed by timed intercourse or intrauterine insemination for subfertility associated with polycystic ovary syndrome," Cochrane Database of Systematic Reviews. 2017;1:1.
27. Azziz R. Controversy in clinical endocrinology: diagnosis of polycystic ovarian syndrome: the Rotterdam criteria are premature. J Clin Endocrinol Metab. 2006;91(3):781-5.
28. Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism. 1994;43(5):647-54. doi:10.1016/0026-0495(94)90209-7.
29. Al-Ozairi E, Quinton R, Advani A. Therapeutic response to metformin in an underweight patient with polycystic ovarian syndrome. Fertil Steril. 2008;90(4):e1-e4. doi:10.1016/j.fertnstert.2007.11.041.
30. Li Y, Chen C, Ma Y, *et al*., "Multi-system reproductive metabolic disorder: significance for the pathogenesis and therapy of polycystic ovary syndrome (PCOS)," Life Sciences. 2019;228:167-175.
31. Glueck CJ, Moreira A, Goldenberg N, Sieve L, Wang P. "Pioglitazone and metformin in obese women with polycystic ovary syndrome not optimally responsive to metformin," Human Reproduction. 2003;18(8):1618-1625.