EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 7
457-465
Year: 2020

A COMPARATIVE STUDY TO EVALUATE THE EFFECTIVENESS OF METFORMIN AND MYOINOSITOL IN THE TREATMENT OF PCOS

Dr. Rekha Garlapati[1]*, Dr. Ashish Agarwal[2], Dr. R. Nishanth[3], Dr. Y. Rupa[3] and Dr. T. Lakshmi Teja[3]

[1]*MD, Gynecology, Department of Obstetrics & Gynecology Durgabai Deshmukh Hospital and Research Centre Andhra Mahila Sabha, Vidyanagar, Hyderabad.
[2]Prof. & HOD, Dept. of Pharmacology, Bharat Institutions, Mangalpally, Ibrahimpatnam, Hyderabad.
[3]Pharm –D Students, Bharat College of Pharmacy, Mangalpally, Ibrahimpatnam, Hyderabad.

***Corresponding Author: Dr. Rekha Garlapati**
MD, Gynecology, Department of Obstetrics & Gynecology Durgabai Deshmukh Hospital and Research Centre Andhra Mahila Sabha, Vidyanagar, Hyderabad.

Article Received on 05/05/2020 **Article Revised on 25/05/2020** **Article Accepted on 15/06/2020**

ABSTRACT

Introduction: In polycystic ovary syndrome (PCOS), changes in physical appearance i.e. weight gain, hirsutism, menstrual disturbances and infertility result in reduced quality-of-life. Metformin and Myoinositol being insulin sensitizers improve biochemical, clinical and reproductive parameters in PCOS in women. This study was done to compare the efficacy and safety of Myo inositol versus metformin in PCOS in women. **Objective:** The primary objective of the study was to study the effect of metformin and myoinositol in the regulation of menstrual cycles. **Methodology:** A prospective observational study was conducted on 60 patients at DURGABAI DESHMUKH HOSPITAL AND RESEARCH CENTRE, HYDERABAD in department of Gynaecology for a period of six months. **Results:** There was significant improvement in all the symptoms in both the groups over a period of 6months. However, on comparing both the groups after 6 months, no significant difference was observed in all the symptoms. regulation of menstrual cycles was better with Myo-inositol as compared to Metformin. **Conclusion:** Our study was to compare the effectiveness of myoinositol versus metformin in PCOS patients. Using clinical assessment, we have shown that myoinositol and metformin, both the drugs resulted in significant weight loss, regularisation of menses. In women with the PCOS, insulin resistance is related to a deficiency in myoinositol containing mediator of insulin action and the administration of the myo-inositol improves insulin sensitivity to conclude, metformin is effective in reducingthe metabolic and hormonal parameters and also improves fertility but myoinositol not only improves all the above parameters but also decreases insulin resistance. Myoinositol also has better patient compliance and well tolerated than metformin.

KEYWORDS: Myoinositol, metformin, polycystic ovarian disease.

1.0 INTRODUCTION

The term Polycystic Ovarian disease(PCOD) was first described by Irving Stein and Michael Leventhal as a triad of 'Amenorrhea', 'Obesity' and 'Hirsutism'. In 1935 whenthey observed therealtion between obesity and reproductive disorders.[1] It is hence also known as the 'Stein-Leventhal Syndrome' or 'Hyperandrogenic Anouvulation' (HA) and is the most common endocrine ovarian disorder affecting approximately 2-8% women of reproductive age world wide.[2] It is also referred to as the syndrome O i.e., Overnourishment, Overproduction of Insulin, Ovarian confusion and Ovulatory disruption. So, PCOD is called as Polycystic Ovarian Syndrome (PCOS).

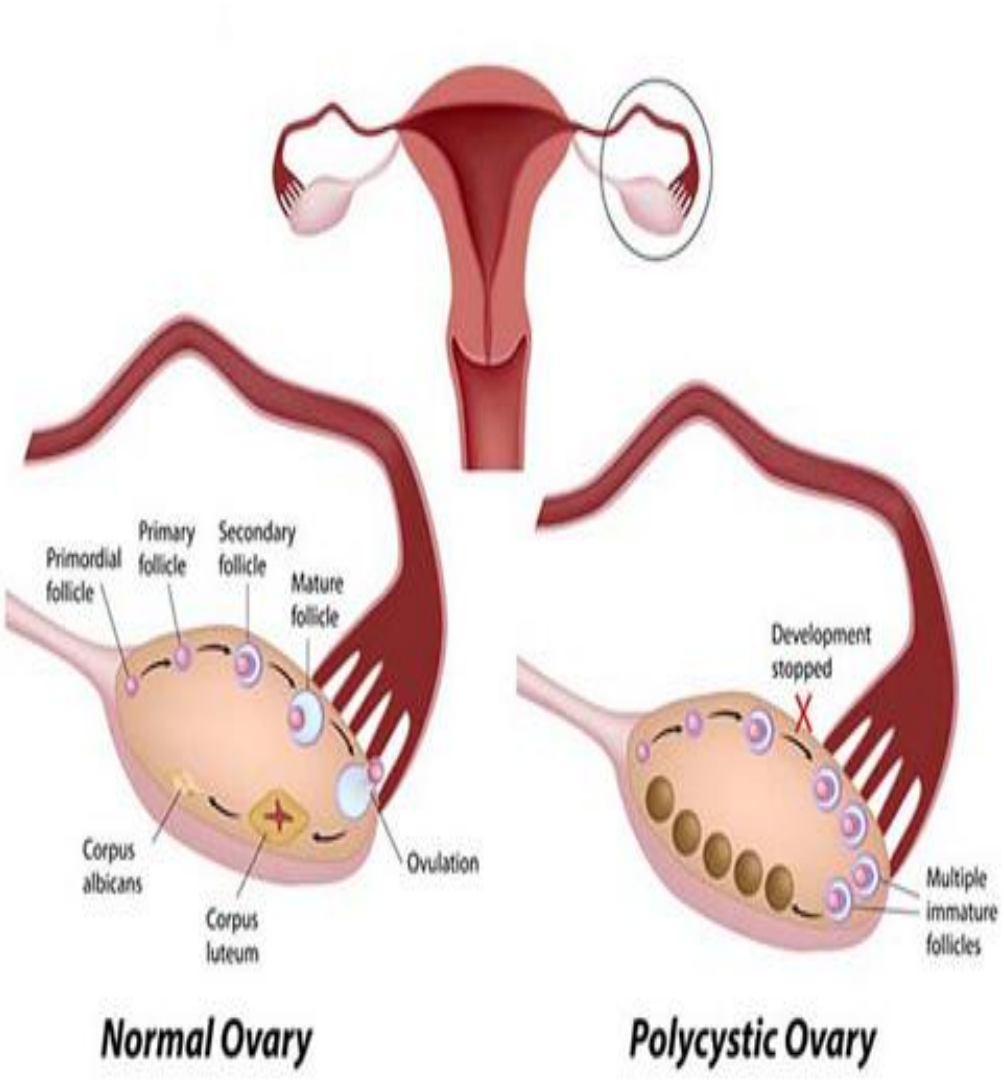
PCOS is currently considered as a lifestyle disorder affecting 2.2-26% of young girls in their reproductive age in India. Though globally it is an alarming incidence, its diagnosis is difficult as it manifests as a spectrum of symptoms than a specific one. It is primarily characterized by an extremely irregular menstrual cycle in which ovulation may not occur.[3] Normal pubertal events include oligomennorhea, hirsutism, acne andweight gain. No single criterion is sufficient for clinical diagnosis due to multiple aetiologies and presentations.[3]

PCOS is a common disorder, often complicated by chronic anovulatory infertility and hyperandrogenism with the clinical manifestation of oligomennorhea, hirsutism and acne.[4] Many women with this condition are obese and have a higher prevalence of impaired glucose tolerance, type 2 diabetes and sleep apnoea than is observed in the general population. They exhibit an adverse cardiovascular risk profile, characteristic of the cardiometabolic syndrome as suggested by a higher reported incidence of hypertension, dyslipidaemia,

visceral obesity, insulin resistance andhyperinsulinaemia.[5]

PCOS prevalence worldwide is estimated to be 6-10% or even 15% when the diagnosis is based on Rotterdam criteria.[6] Studies of PCOS in India carried out in convenience samples reported a prevalence of 3.7% to 22.5%[7,8], with 9.13% to 36% prevalence in adolescents only.[9,10]

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women and major cause of anovulatory infertility. PCOS patients can present a wide range of signs and symptoms.Diagnosis of PCOS is currently based on the criteria of the ESRHE/ASRM. Rotterdam consensus meeting in 2003[11], which broadened the previous NIH classification of 1990.[12] It based on at least two of the following features: oligoanovulation, hyperandrogenism and polycystic ovaries by ultrasound.[11] The AES criteria require clinical and/or biochemical hyperandrogenism simultaneously with oligo/anovulation and ultrasonographic evidenceof polycystic ovaries. Aetiology of PCOS is not completely understood yet, PCOS is considered a multifactorial disorder with various genetic, metabolic, endocrine and environmental abnormalities.[13]



NEEED FOR THE STUDY

- Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among reproductive-aged women and is characterized by hyperandrogenemia, menstrual dysfunction, and polycystic ovarian morphology. The hormonal abnormalities inherent in PCOS often begin in adolescence and include hyperinsulinemia and rapid luteinizing hormone (LH) pulse frequency, both of which mediate ovarian and adrenal overproduction of androgens. Although differences exist regarding the diagnostic criteria for PCOS, hyperandrogenemia is the final common pathway for the development of adolescent PCOS. Recognizing and reducing androgen levels in

adolescence is critical given their association with the metabolic syndrome.

- In women of Indian subcontinent, prevalence rates as high as 50% have also been detected and is a leading cause of infertility, primarily secondary to anovulation.
- Guideline released by endocrine society state that metformin has limited or no benefit in treating hyperandrogenism and should be used if patients presenting with menstrual irregularity as the chief complaint. The applicability of these guidelines in south Asia particularly in India is uncertain because of high prevalence of insulin resistance amonthis population. Where patients with PCOS of south Asia ethnicity had severe symptoms, higher fasting insulin concentrations and low insulin sensitivity compared with Caucasians. Thus insulin sensitizing drugs may have more beneficial role to play in these population.
- Myoinositol is also prescribed for the treatment of metabolic disturbances in PCOS patients however the cost of Myoinositol is more and thus may not be affordable by all the patients.
- There are only few studies carried out comparing these drugs.
- Hence this study is planned to compare the effectiveness and safety of Metformin and Myoinositol.

MATERIALS AND METHODS

The experimental design was divided into 5 parts as follow:
Clinical Study Methodology
Ethical Considerations
Efficacy Measurements
Safety Measurements
Statistical Analysis

CLINICAL STUDY METHODOLOGY

Objective

The primary objective of the study was to study the effect of metformin and myoinositol in the regulation of menstrual cycles.

Study Design

This was a prospective observational study.

Number of Subjects

Enough patients were screened and enrolled so as to have data on 60 completed patients. Drop-outs and withdrawal were not replaced. Data is presented on all completed subjects.

Selection of Subjects

Adequate numbers of patients were selected from Durgabai Deshmukh Hospital and research centre in Department of Gynaecology. All the patients underwent a standardized screening procedure.

Screening Assessments

Medical histories and demographic data, including, Age, Height, Weight were recorded. Each patient underwent the following tests,

- Ultrasound scan of abdomen
- GTT

Only patients who met following inclusion criteria were enrolled. A total of 60 patients were selected based on the following inclusion and exclusion criteria:

Inclusion Criteria

- In the age range of 18-45 years.
- Patients confirmed with PCOS according to AES (Androgen Excess Society)/2006 criteria: Presence of hyperandrogenism (clinical and/or biochemical), Oligo or anovulation, PCOM (Polycystic ovarian morphology)- at least one ovary with 12 or more follicles (2-9 mm in diameter) or ovarian volume >10 ml and those willing to give a written informed consent.

Exclusion Criteria

- Patients below 18 or above 45 years.
- Pregnant women
- Patients on other treatment for PCOS
- Patients who are not willing for treatment.
- Patients with hyperprolactinemia

Dosing, Admission and Stay

Since this was a observational study conducted in the out-patient department, the study subjects were not admitted. Patients were monitored for the adverse events by interviewing.

Treatments

The patients were treated with following either metformin or myoinositol for three month:
Myoinositol: 4 grams/day.
Metformin: 500mg tablets twice daily.

Assessment of Compliance

Compliance was assessed by interviewing and questioning the patients during the study period.

Restrictions

Medications

All patients were instructed not to take any other medications, unless otherwise those prescribed by investigator, including OTC during the study period. The patients were advised to take medication by investigator only in case of medical emergencies.

ETHICAL CONSIDERATIONS

Basic Principles

This research was carried out in accordance with the basic principles defined in the International Conference on Harmonisation “Guidance for Good Clinical Practice” and the principles enunciated in the Declaration of Helsinki.

Institutional Review Board

This protocol and the corresponding informed consent form (ICF) used to obtain informed consent of study patients were reviewed and approved by the Ethics committee of DDHRC scientific Review Board.

The version 2 of the protocol and the ICF for this study were reviewed and approved by DDHRC Ethics Committee on 25th September 2016.

Informed Consent

The purpose of the study, procedures to be carried out, potential hazards and rights of the patients were described to the patients in non-technical terms before the patients were enrolled into the study. All the patients provided formal written consent after attending an oral presentation and after thoroughly reading the version 2 of the Informed Consent Form.

Drop-out/ Withdrawal of Subjects from Study

Patients were informed that they are free to drop-out from the study at any time without stating any reason. The decision of withdrawal of a patients from the study were considered for any of the following reasons:

(i) The patients suffers from significant intercurrent illness or undergoes surgery during the course of the study.

(ii) The patient experiences adverse event, and withdrawal is in the best interest of the subjects.

(iii) The patient fails to comply with the requirements of the protocol.

Details of reasons for withdrawal of subjects were recorded and reported. Every effort was made to obtain a complete follow-up for any withdrawn subject.

Study Documentation

All data collected during the conduct of the study was directly entered in the data recording form including laboratory data for their records.

EFFICACY MEASUREMENTS

The primary efficacy parameters was regulation of menstrual cycle.

SAFETY MEASUREMENTS

All the patients were monitored throughout the study period for adverse events. Patients were specifically asked about any adverse events on each hospital visit.

STATISTICAL ANALYSIS

- Results are presented as mean ± S.D.
- The demographic and other baseline characteristics of the patients (e.g. age, BMI) are summarized in the table.
- Change from baseline were calculated for BMI. Whenever change from baseline was calculated, only those patients for whom baseline and post-treatment assessment (at 3 month) are available were included in the analysis.
- Student t-test was used to compare the baseline and post-treatment values for each variable. The significance of difference was assessed at $p < 0.05$. Both intragroup and intergroup statistical analysis was done. Intragroup analysis for repeated measures was done using paired t-test. Intergroup analysis was done using paired t-test of unequal variance. Categorical data like number of patients having regular menstrual cycle in both the groups were represented using bar and pie diagrams.

RESULTS

This prospective observational study was conducted after the protocol and the informed consent form (ICF) were reviewed and approved by scientific and ethical committee of Durgabai Deshmukh Hospital and research centre. The detail procedure followed in this study have been described in the approved protocol "Comparative study to evaluate the effectiveness of metformin and myoinositol in the treatment of polycystic ovarian syndrome". The purpose of the study, details of the procedures involved and potential risks that may be encountered during the study were lucidly explained to the patients in the vernacular language and non-technical terms. After the patients attended the oral presentation and had thoroughly read the version one of the informed consent form, formal written consent was obtained from all the patients before they were enrolled into the study.

A total number of 60 Patients with PCOD were screened according to the inclusion and exclusion criteria. Out of these, 30 patients took myoinositol 4g/day and remaining 30 patients took metformin 500mg/day.

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The study was conducted in the Indian population. The mean age of the patients was 48.23 years. Detail demographic details of the patients is presented in Table 3.

Table 1: Demographic and baseline characteristics of the patients.

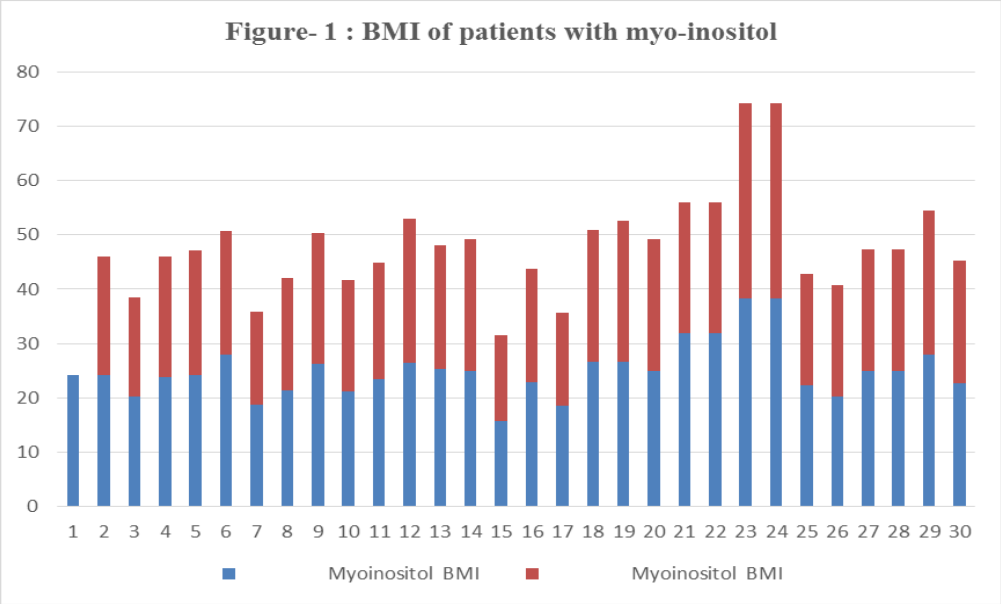
S.No	Variables	Group A (n=30)	Group B (n=30)	P-value
1	Age	**24.9±3.79**	**25.33±3.83**	**NS**
2	BMI	**25.04±5.03**	**26.19±4.16**	**NS**

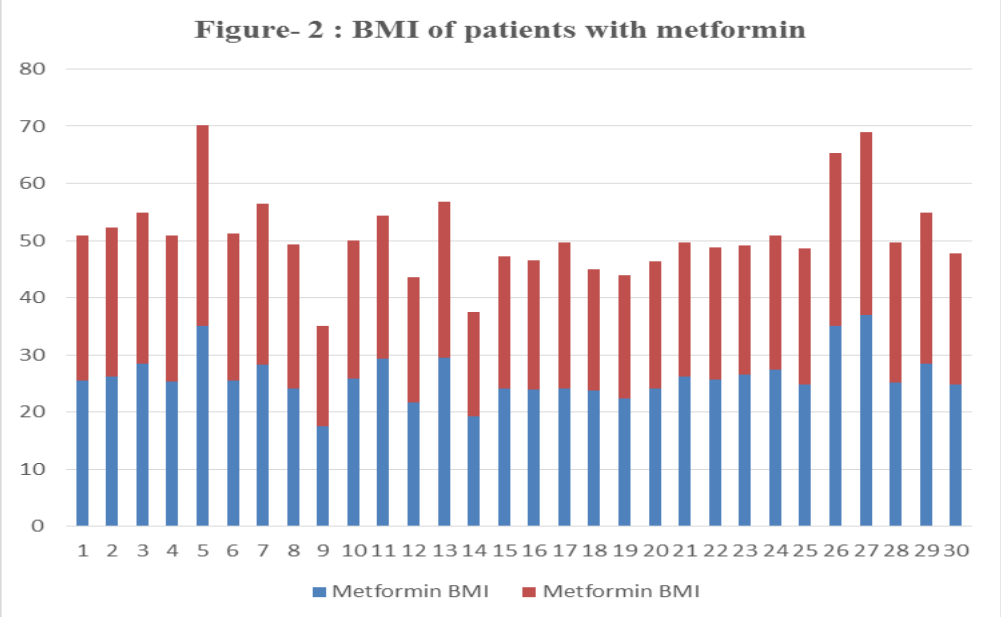
- Age and BMI are expressed as Mean ± SEM.
- Group-A: Myo-inositol 4g/day.
- Group-B: Metformin 500mg/day.

Table- 2: Comparison of changes in BMI in both the groups.

	Group-A (n=30)	Group-B (n=30)
Before Treatment	25.04±5.03	26.19±4.16
After Treatment	23.00± 4.36	24.16±3.59

- All values are expressed as Mean ± SEM.
- Group-A: Myo-inositol 4g/day.
- Group-B: Metformin 500mg/day.





INTRA GROUP ANALYSIS

- Comparison of BMI before and after the treatment with myoinositol are not statistically significant. ($p > 0.05$)
- Comparison of BMI before and after the treatment with metformin are not statistically significant. ($p > 0.05$)

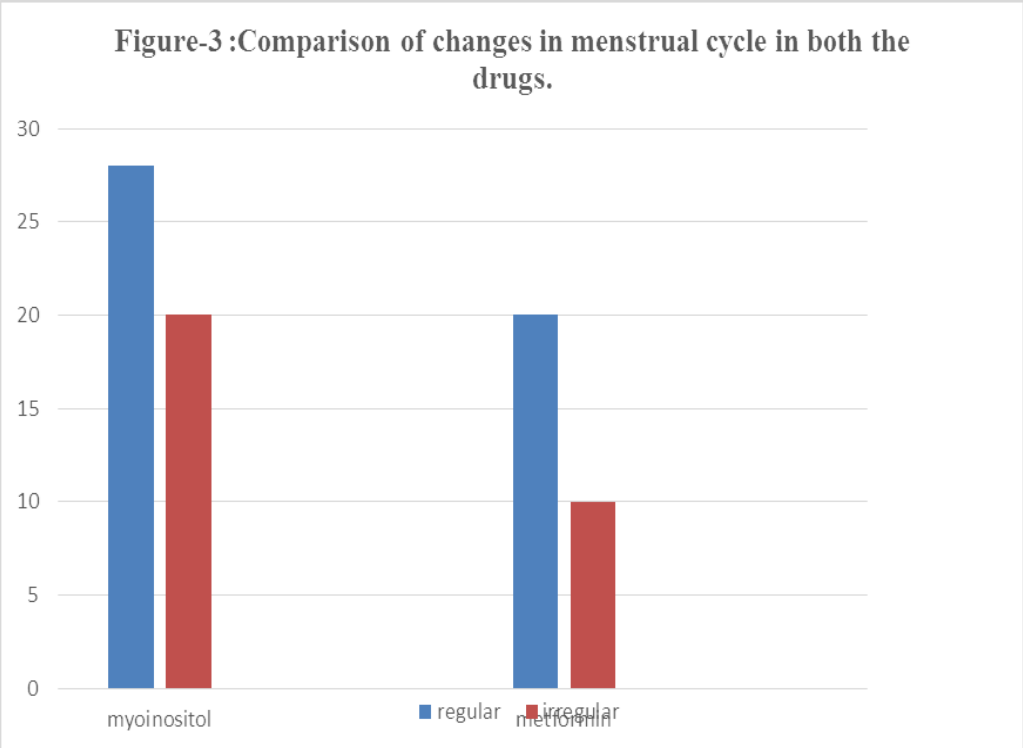
INTER GROUP ANALYSIS

- Comparison of BMI between Group-A and Group-B after the treatment is not statistically significant. ($p > 0.05$)

Table- 3: Comparison of changes in menstrual cycle in both drugs.

Menstrual History	Group-A (n=30)	Group-B (n=30)
Irregular	30	30
Regular	28	20

- Group-A: Myo-inositol 4g/day.
- Group-B: Metformin 500mg/day



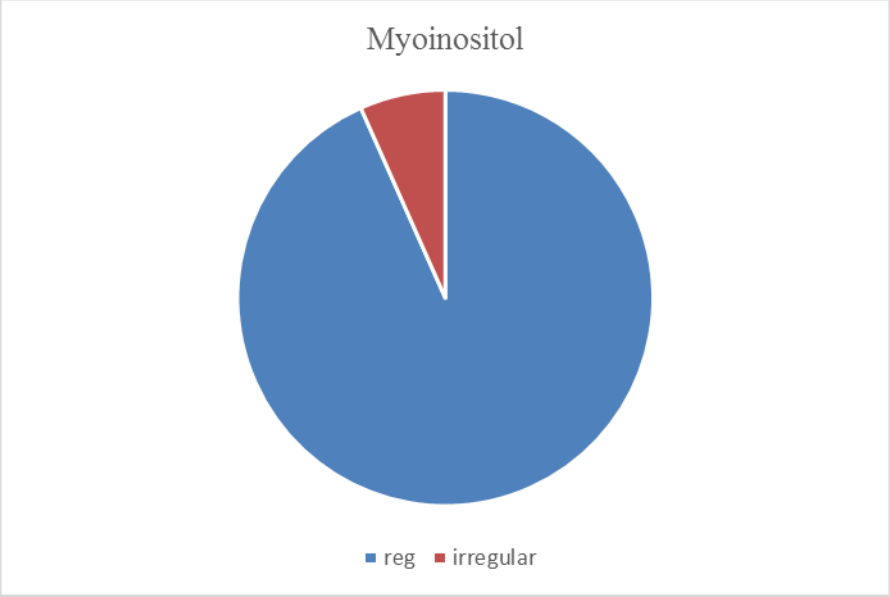


Figure-4: Comparison of changes in menstrual cycle with the treatment of Myoinositol.

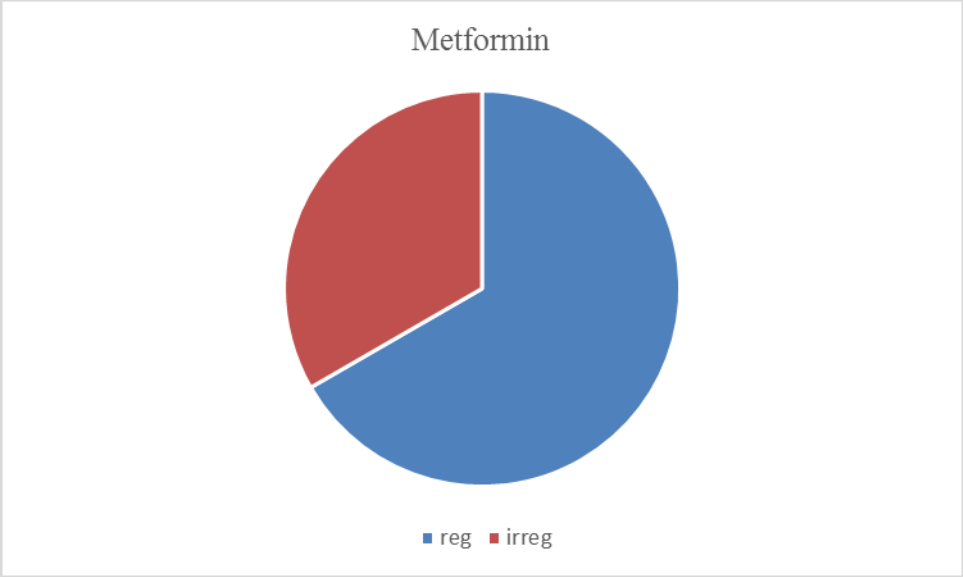


Figure-5: Comparison of changes in menstrual cycle with the treatment of Metformin.

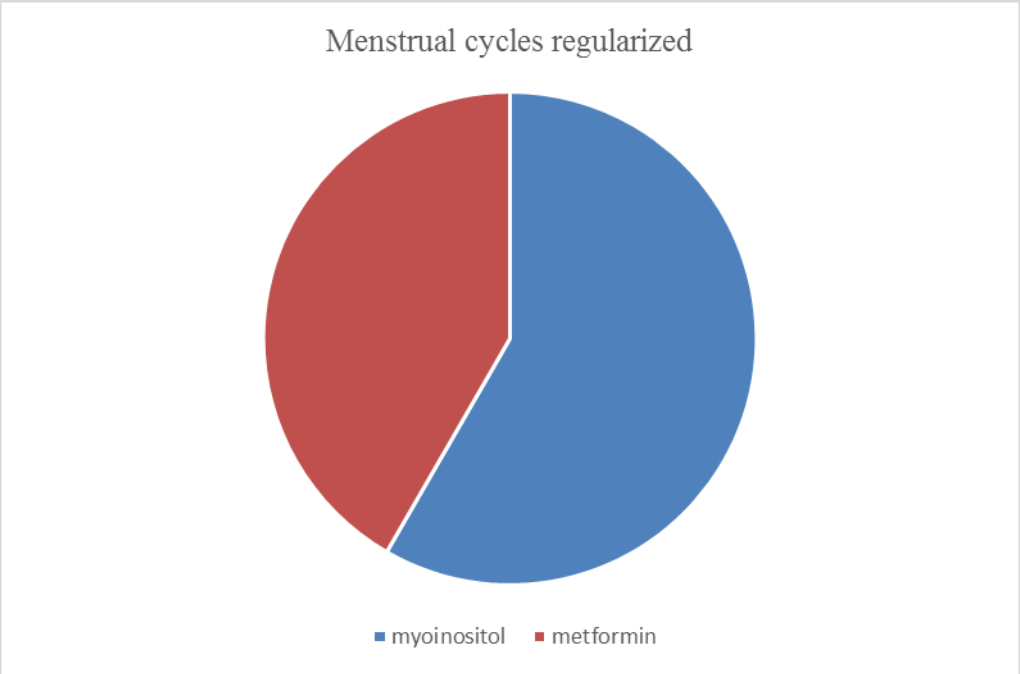


Figure-6: Comparison of changes in menstrual cycles in both the drugs.

DISCUSSION

PCOS is one of the most common endocrine disorders affecting women, it is the most common cause of female infertility and it is characterized by a combination of hyperandrogenism, chronic anovulation and irregular menstrual cycle.[140,141] In about 50% of patients with PCOS, insulin receptor phosphorylation is impaired.[142] Insulin seems to be involved in the dysregulation of Lutenizinghormone (LH) secretion, promote ovarian androgen secretion by enhancing cytochrome P450C17 activity to affect the normal follicular growth, decrease serum sex hormone binding globulin (SHBG) synthesis by liver, thereby increasing free androgen levels. It also potentiates in vivo adrenocorticotrophic hormone (ACTH) stimulated adrenal androgen production in women with PCOS.[143]

Several trials showed that insulin sensitizer agents, such as metformin and MI, are the firstline treatment to restore normal menstrual cycles in women suffering from PCOS[144-148] suggesting that an endocellular defect of the precursor of IPG such as MI and/or DCI might trigger the compensatory hyperinsulinemia in most PCOS subjects.

In PCOS, ovarian dysfunction usually manifests as oligomenorrhoea/ amenorrhoea resulting from chronic oligo-ovulation/anovulation.[149] The majority of PCOS patients have ovarian dysfunction, with 70% to 80% of

women with PCOS presenting with oligomenorrhoea or amenorrhoea. The clinical and/or biochemical signs of androgen excess in PCOS result from increased synthesis and release of ovarian androgens. PCOS is a common cause of hirsutism occurring in approximately 60% of cases, however this varies with race and degree of obesity.[150] Hirsutism should be assessed with a standardised scoring system i.e. modified Ferriman-Gallwey (mFG) score, which is also used in India.[151]

In this study, total no. of 60 patients with irregular menstrual cycles were enrolled and were treated with either myoinositol or metformin. All patients received either myoinositol 4g/day (n= 30) or metformin 500 mg/day (n=30). Of the total number of patients enrolled, 70% are unmarried. This correlates that PCOS mostly occurs in young females.

As the difference in all these parameters after 3 months of respective treatment in both the groups was found to be statistically non-significant, thus, myo-inositol may be considered comparably effective to metformin in treatment of PCOS as the regulation of menstrual cycle is more with myoinositol compared to metformin.

Treatment with metformin and myoinositolwas well tolerated. There were no adverse events reported.

Limitations: Some of the limitations that should be taken into consideration while interpreting the results of this study are:

1. Limited sample size: While planning this study, no formal calculation was done to estimate the number of patients required. The total number of patient was considered based on the feasibility and the limited time that was available to complete the study.
2. Duration of the study: The study was of 6 month duration. This limited duration of the study might have not allowed to reach the maximum effect with metformin and myoinositol. Hence, future studies with long-term duration are recommended.
3. Myoinositol is a costly medicine and cannot be affordable by some patients.
4. This was an observational study.

CONCLUSION

Aim of our study was to compare the effectiveness of myoinositol versus metformin in PCOS patients. Using clinical assessment, we have shown that myoinositol and metformin, both the drugs resulted in significant weight loss, regularisation of menses. In women with the PCOS, insulin resistance is related to a deficiency in myoinositol containing mediator of insulin action and the administration of the myo-inositol improves insulin sensitivity to conclude, metformin is effective in reducingthe metabolic and hormonal parameters and also improves fertility but myoinositol not only improves all the above parameters but also decreases insulin resistance.

Myoinositol also has better patient compliance and well tolerated than metformin. These beneficial effects of inositol support a future therapeutic role in women with PCOS. Inositol deficiency is the basic pathophysiology for PCOS, hence inositol supplementation is essential in the management of PCOS to improve insulin sensitivity.

PCOS is not only a health hazard but also an economic burden. Based on the above observations it can be said. that, since the clinical features of PCOS are heterogeneous, they have to be investigated accordingly, for selection of appropriate treatment modality. Early identification of high risk cases and timely therapeutic intervention can halt this on-going process and prevent long term complications. This study conducted at Durgabai Deshmukh Hospital and Research Centre in 60 patients demonstrated that Myoinositoleffectively and safely restores regular menstrual cycles. Thus myoinositol provide effective and well-tolerated treatment for PCOS.

REFERENCES

1. Stein IF, Leventhal MN. Amenorrhea associated with bilateral Polycystic Ovaries. American Journal of Obstetrics and Gynaecology, 1935; 29: 181.
2. Knochenhauer ES. et al. Prevalance of Polycystic Ovarian Syndrome. Journal of Clinical Endocrinology and Metabolism, 1998; 83(9): 3068-3082.
3. Azziz R et al. The Prevalence and feautes of Polycystic Ovarian Syndrome in an unselected population. Obstetric and Gynaecology, 2004 Jun; 89(6): 2745-2749.
4. Franks S. Polycystic Ovary Syndrome. N Engl J Med., 1995; 333: 853-61.
5. Glueck CJ, Papanna R, Wang P, Goldenberg N, Sieve-Smith L. Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome. Metabolism, 2003; 52: 908-15.
6. Tehrani FR, Simbar M, Tohidi M, Hesseinpanah F, Azizi F. The prevalence of polycystic ovary syndrome in a community sample of Iranian population. Iranian PCOS prevalence study. Reprod Biol Endocrinol, 2011; 39: 1-7.
7. Gill H, Tiwari P, Dabadghao P. Prevalence of polycystic ovary syndrome in young women from North India: A Community-based study. Ind J Endocrinol Metab., 2012; 16(Suppl 2): S389-S92.
8. Joshi B, Mukherjee S, Patil A, Purandare A, Chauhan S, Vaidya R. Across-sectional study of polycystic ovarian syndrome among adolescent and young girls in Mumbai, India. Ind J Endocrinol Metab., 2014; 18(3): 317-24.
9. Nidhi R, Padmalatha V, Nagarathna R, Amritanshu R. Prevalence of polycystic ovarian syndrome in Indian adolescents. J Pediatr Adolesc Gynecol, 2011; 24: 223-7.
10. Nair MK, Pappachan P, Balakrishnan S, Leena ML, George B, Russell PS. Menstrual irregularity and

polycystic ovarian syndrome among adolescent girls- a 2 year follow-up study. Indian J Padiatr, 2012; 79(Suppl 1): S69-S73.
11. The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group.
12. Revised 2003 consensus on diagnostic criteria and long-term health risk related to polycystic ovary syndrome (PCOS). Hum Reprod, 2004; 19: 41–7.
13. Zawadski Jk, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, givens JR, Haseltine F, editors. Polycystic ovary syndrome. Boston: Blackwell scientific, 1992; 377-84.
14. Franks S, Mc Carthy M, Hardy K. Development of polycystic ovary syndrome: involvement of genetic and environmental factors. Int J Androl, 2006; 29: 278–85.