

DOI: <http://dx.doi.org/10.18203/2320-1770.ijrcog20190286>

Original Research Article

Prevalence and predictors of metabolic syndrome with comparison of myoinositol and metformin in PCOS women

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Received: 03 December 2018

Accepted: 29 December 2018

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ABSTRACT

Background: The objective is to determine the prevalence of metabolic syndrome (MBS) and the effects of insulin sensitizers to improve the clinical and hormonal milieu for better reproductive outcome in PCOS women.

Methods: This prospective cross-sectional study was conducted on 50 PCOS women and 50 age matched control to determine the prevalence of the MBS in two tertiary hospitals over one year. Diagnosis of PCOS was based on at least two of ESHRE/ASRM criteria and diagnosis of MBS was based on at least three of NCEPATPIII criteria. Patients already diagnosed as PCOS were treated with insulin sensitizers myoionositol and metformin which were compared.

Results: The study revealed that the prevalence of MBS was 40 % (20/50) nearly 4-fold higher than that of control groups. Among PCOS women, the most prevalent MBS factors were high BMI (52%) and low serum HDL-C (42%). The least prevalent factor was high fasting serum glucose level (16%). The resumption of spontaneous regular menstrual cycle and pregnancy rate in infertile groups of PCOS patients with myoionositol and metformin were 61% vs. 26% and 50% vs. 91% respectively. The myoionositol group did not require any extra ovulating agents for pregnancy, while 7 out of 11 patients in metformin group needed clomiphene citrate for ovulation induction to achieve pregnancy. With myoionositol there is significant reduction of weight, BMI, LH/FSH ratio and fasting insulin level; whereas metformin shows decrement of weight and BMI only.

Conclusions: The prevalence of MBS in PCOS is nearly 4 times in present study and there is significant improvement of symptom profile, weight, BMI and change of hormonal pattern in myoionositol group.

Keywords: BMI, Metabolic syndrome, Myoionositol, Metformin, Polycystic ovarian syndrome

INTRODUCTION

Polycystic ovarian disease (PCOS) is one of the most common endocrinopathies affecting 4% to 7% of women in reproductive age.¹ It is associated with clinical presentations including hirsutism, menstrual irregularities and infertility. PCOS have hyperandrogenemia, elevated luteinizing hormone (LH), and normal or decreased follicle stimulating hormone (FSH). The Diagnosis of PCOS is based on the presence of any two of the following three components of Rotterdam European Society for Human Reproduction and Embryology/ The American Society of Reproductive Medicine

(ESHRE/ASRM)-sponsored PCOS consensus workshop group revised 2003 criteria; oligoovulation, and or anovulation, hyperandrogenism (clinical and /or biochemical) and polycystic ovaries (ultrasonographical) in absence of other causes of hyperandrogenism.² Metabolic syndrome (MBS) which is also called insulin resistance syndrome or syndrome 'X' is also responsible for much of the excess cardiovascular disease morbidity among overweight and obese patients and those person with type 2 diabetes mellitus.³ A number of expert groups have attempted to develop a unifying definition for the MBS. One of the most widely accepted of these definitions have been produced by The National

Cholesterol Education Program- Third Audit Treatment Panel (NCEP ATP III) (Executive Summary of the third report of the national cholesterol education program, 2001).⁴

According to this programme MBS includes the presence of any three or more factors of the five components increased waist circumference (≥ 88 cm), high fasting plasma glucose level (≥ 110 mg/dl), increased blood pressure ($\geq 130/85$ mm of Hg), serum triglyceride level ≥ 150 mg/dl and low serum HDL cholesterol level (< 50 mg/dl).

The metabolic syndrome is associated with higher risk of atherosclerosis, cardiovascular disease, thromboembolic events and mortality.^{1,5} A few studies conducted the world wide looking for the prevalence of MBS among PCOS patients were within the range of 14.5% to 46.0%, however, the prevalence was reported to be as high as 47.3%.⁶⁻⁸

PCOS is a reproductive problem and these patients were treated based on its significant aspect. Insulin sensitizers (metformin, glitazones) and anti-obesity drugs (sibutramine, orlistat etc) have been extensively studied.⁹ Myoinositol and berberine are the newer insulin sensitizing agents that are useful for correcting biochemical abnormalities and restoring ovarian function instead of using older methods of hormones therapy for ovarian suppression and cycle regulation.^{10,11}

The aim of the study was to determine the prevalence of metabolic syndrome (MBS) and its main determinance in women with PCOS along with the evaluation of clinical and hormonal improvement with reproductive outcome by the use of insulin sensitizers metformin and myoinositol.

METHODS

The prospective cross-sectional study was conducted on 50 cases diagnosed as PCOS and compared with 50 healthy age matched women (control group) in the reproductive age group of 17-40 years over one year (2016-2017) in the Dept of Obstetrics and Gynecology of RG. Kar Medical College and Burdwan Medical College.

The diagnosis of PCOS was based on any two of the following three criteria.² These are:

- Oligo and/or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries as confirmed by USG

Inclusion criteria

- Age groups 17-40 years
- Diagnosed cases of PCOS
- Apparently healthy woman without PCOS.

Exclusion criteria

- Patients who were diabetic and hypertensive or having thyroid dysfunction.
- Hyperprolactinemia, non-classical congenital adrenal hyperplasia (NCCAH), Cushing's syndrome, acromegaly or use of medications known to affect sex steroid metabolism, such as oral contraceptive pills or insulin sensitizing drugs and other hormonal agents known to affect menstrual cycle for at least 3 months before collection of samples.

After taking written consent in local languages, careful history and clinical examination of height, weight, waist circumference, waist-hip ratio and blood pressure was measured.

The marker of obesity is determined by BMI and waist hip circumference. Height and weight are used for calculation of BMI (weight in kg/height in m²). Waist circumference in centimetre was measured at a point midway between the lowest rib and the iliac crest using a soft non-stretchable tape and was taken at the end of normal expiration while hip circumference is taken at the level of greater trochanter. Waist-hip ratio > 0.85 is considered abnormal. For assessment of MBS in the PCOS group the NCEPATPIII guideline was used.⁴

Patients who are already diagnosed as PCOS (n=50) are treated with the drugs and are compared in this study. After randomization by computer generated numbers each group comprised of 25 patients, each receiving the following treatment. Group A: Myoinositol (1g/day), Group B: Metformin: 1gm/day and the treatment were continued for 6 months with proper discussion of the subjects like the procedure of drug intake, possible side effects and follow -up examinations. Base line investigations as complete hemogram, blood sugar and oral glucose tolerance test (OGTT), fasting insulin, lipid profile, and hormonal estimation of LH, FSH, testosterone and estrogens were carried out. The hormone levels were measured on 2nd or 3rd day of a spontaneous or induced menstruation.

According to marital status trans abdominal or trans vaginal USG was chosen to diagnose ovarian volume, endometrial thickness and a mid-cycle USG was done to look for spontaneous ovulation in the 3rd or 4th month. At the end of 4th month the ovaries are also examined by USG for detection of ovarian volume, number of ovarian follicles and base line investigations of FSH, LH, fasting blood sugar and fasting insulin were repeated again with clinical measurement of waist hip ratio.

The primary outcome measure in the study is focussed on resumption of spontaneous regular cycle in women with oligo /amenorrhea and pregnancy rate in infertile patient.

The secondary outcome measure compared at enrolment and after treatment were:

- Clinical parameters: Weight, BMI, acne and hirsutism
- Laboratory parameters: Fasting insulin, LH/FSH ratio
- Ultrasound appearance of ovaries.

Statistical analysis

The sample size was calculated based on the formula, $n = Z^2 \times (p) \times (1-p) / \Delta^2$, where n = the sample size; Z= Z value (e.g. 1.96 for 95% confidence level); Δ is the confidence interval i.e. 0.04 for ±4% and p=percentage picking a choice i.e. 5%, expressed as decimal to 0.05. Data entry

and statistical analysis was done in Microsoft excel and Stat calc 7 (version 7.1.1). Means and standard deviation was done for numerical variable and the student’s t test was used for between -group comparisons of continuous variable. P value of <0.05 was considered to be statistically significant.

RESULTS

A total of 100 pregnant women participated in this study. Fifty women having PCOS and 50 women without PCOS in the reproductive age group of 17-40 years were selected. The clinical data of women with PCOS and controls are depicted in Table1.

Table 1: Clinical data in women with PCOS and in normal controls.

	Age (years)	BMI (Kg/m ²)	WC (cm)	SBP (mm of Hg)	DBP (mm of Hg)
Normal control women (mean±SD)	25.89±4.49	24.50±2.83	77.72±8.29	120±10.27	78±7.24
PCOS (mean±SD)	25.80±4.09	26.03±3.08*	83.26±10.44**	125± 14.85***	80±9.21

BMI: body mass Index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure. *P<0.011, **P<0.004, ***P<0.053

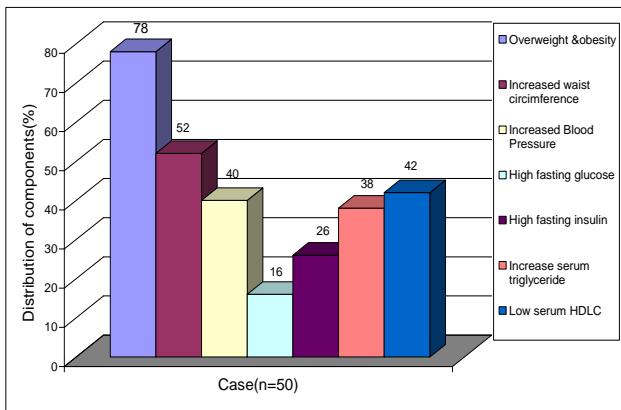


Figure 1: Distribution of different components of the metabolic syndrome in women with PCOS (n=50).

Patients with PCOS had higher BMI (26.03 Kg/m² vs 24.50 Kg/m²), waist circumference (83.26 cm vs

77.72cm) and systolic blood pressure (125mm of Hg vs 120mm of Hg) when compared with normal women.

Seventy eight percent of PCOS women were overweight and obese and 9 (18%) had normal weight. Increased waist circumference (>88cm) and blood pressure ≥130/85 mm of Hg were noted in 52% and 40 % of PCOS women respectively (Figure 1).

Women with PCOS had higher fasting insulin (18.47 μU/ml vs 14.12 μU/ml), triglycerides (136.88 mg/dl vs 115.7 mg/dl) and lower HDL cholesterol (51.64 mg/dl vs 55.52mg/dl) than normal control of the same age (Table 2). In PCOS women increased blood glucose (>110mg/dl) and fasting insulin (≥ 25μIU/ml) were noted in 8 women (16%) and 13 women (26%) respectively. Low HDL-cholesterol (< 50 mg/dl) was found in 21 women (42%) while only 19 women with PCOS (38%) had increased triglyceride level (>150 mg/dl) (Figure 1).

Table 2: Metabolic data in women with PCOS and in normal controls.

	Fasting insulin (μU/ml)	FBG (mg/dl)	HDL-C (mg/dl)	Triglyceride (mg/dl)
Normal control women (mean ± SD)	14.12±4.08	78.14±11.00	55.52±6.33	115.7±31.35
PCOS (mean ± SD)	18.47±6.64*	82.18±16.34	51.64±7.82**	136.88± 29.77*

*P<0.001, **P<0.008

Table 3 depicts prevalence of individual metabolic abnormalities of the MBS of 50 patients with PCOS. The

most prevalent of the MBS factor in the study subjects were high BMI (26/50; 52%). The least prevalent factor

was high fasting serum glucose level (16%). Low serum HDL cholesterol below 50mg/dl and fasting insulin level

above 25µL/ml were noted in 42% and 26 % of cases respectively.

Table 3: Prevalence of individual metabolic abnormalities of the metabolic syndrome among 50 patients with PCOS.

Metabolic syndrome				
Clinical parameters	Total (n=50) n (%)	Yes (n=20) n (%)	No (n=30) n (%)	P-value
BMI (Waist circumference ≥88cm)	26 (52)	20 (100)	6 (20)	0.001
Triglyceride (≥ 150 mg/dl)	19 (38)	14 (70)	5 (16.67)	0.021
HDL-cholesterol (<50mg/dl)	21 (42)	20 (100)	1 (3.33)	0.001
BP (≥ 130/85mm of Hg)	20 (40)	20 (100)	0 (0)	0.001
FBG (≥110 mg/dl)	8 (16)	8 (40)	0 (0)	0.003
Fasting insulin (≥25µL/ml)	13 (26)	12 (60)	1 (3.33)	0.001

Table4: Primary outcome measure in the myoinositol and metformin groups.

Drugs	Before N (%)	After N (%)	Improvement (%)	P-value
Group A: Myoinositol (n=25)				
Menstrual complains	23 (71.88)	9 (28.13)	60.87	0.001
Infertility	20 (66.67)	10 (33.33)	50.00	0.003
Group B: Metformin (n=25)				
Menstrual complains	19 (57.58)	14 (42.43)	26.31	0.136
Infertility*	11 (91.67)	1 (8.33)	90.91	0.001

* 7 out of 11 patients of infertility needed Clomiphene citrate for ovulation induction with metformin

Table 5: Secondary outcome measure in myoinositol and metformin groups

Clinical parameters of PCOS women Mean (SD)	Group A: Myoinositol (n=25)			Group B: Metformin (n=25)		
	Before	After	P-value	Before	After	P-value
Weight (Kg)	60.95 (8.06)	56.21 (2.84)	0.008	65.62 (6.38)	61.27 (6.43)	0.020
BMI (Kg/m ²)	24.77 (2.98)	21.50 (2.34)	0.001	27.18 (2.74)	25.34 (2.39)	0.015
LH/FSH	3.8 (0.98)	2.20 (0.86)	0.001	2.35 (1.53)	2.29 (1.54)	0.891
Fasting Insulin (µL/ml)	17.37 (6.05)	13.16 (1.02)	0.001	19.47 (7.09)	17 (5.47)	0.174
Ovarian volume (left)cc	11.34 (4.09)	11.35 (4.05)	0.993	11.32 (4.02)	11.31 (4.01)	0.993
Ovarian volume (right)cc	12.34 (3.72)	11.69 (2.31)	0.462	12.63 (3.41)	11.98 (3.01)	0.478

All the parameters were statistically significant. Myoinositol helped in resumption of spontaneous menstrual cycle in 60.87% of women with PCOS having menstrual complaints whereas the same effects in patients who took metformin was only 26.31%. The pregnancy rate in myoinositol and metformin groups were 50% and 90.91% respectively (Table 4).

Table 5 illustrates secondary outcome measure in myoinositol and metformin groups in PCOS women. There is significant improvement of symptom profile like weight loss (61kg to 56 kg), BMI (25Kg/m² to 22 Kg/m²), and significant change in hormonal parameters LH/FSH ratio (4 to 2.2) and fasting insulin (17 µL/ml to 13 µL /ml) levels with myoinositol treatment alone. The outcome of mean body weight and BMI before and after treatment of metformin was statistically significant and found to be 66 kg vs 61 kg and 27 kg/m² vs 25kg/m²

respectively. No significant hormonal changes were noted in metformin group. In both the groups no change was observed on ovarian volumes of either side.

DISCUSSION

This is a prospective cross-sectional study of 100 females attending Gynecological OPD of Burdwan Medical College and Hospital, Burdwan and R.G. Kar Medical College and Hospital, Kolkata over a period of one year.

In present study age of <25 years (26%) and above 26 years (57%) of PCOS patients had a significant associated factor for metabolic syndrome which was similar to other studies.

Weerakiat et al found the prevalence on MBS among PCOS women increased gradually from 22.5% at age <25

years to 53.5% at age >26 years.¹² Dey R et al in their study found that the prevalence of MBS in the age group of 15-25 years was 20.7% whereas it was 71.4% in 25-35 years.¹³

So, age was a significant factor affecting the occurrence rate of MBS amid PCOS patients. Aging women are unable to control weight due to lesser activity, high calorie intake and loss of lean muscles. Fat tissue increases towards the centre of the body, which will give rise to central obesity.

If we compare BMI in cases and controls, it is found that overweight and normal weight subjects in PCOS have higher incidence of lipid profile derangement than their control. Dislipidemia in association with PCOS is a constant observation in other studies.^{7,14-17} In present study among patient with deranged lipid profile, 42% had decreased HDL-C as compared to 14% of control (p=0.002).

Study by Dey R et al showed low HDL-C in 50% of cases.¹³ In present study waist circumference which depicts central obesity >88cm was found in 52% of cases and 18% of control (P=0.001). It is different from the study by Ehrmann et al which supports high value of waist circumference by citing 80% of subjects above 88cm.¹⁷ In the present study fasting insulin level showed increase in 26% of cases and 8% of control (p=0.017). It also shows a significant difference among women with MBS in comparison to those without MBS (P=0.001) as supported by study of Dokra et al.⁸

Prevalence of metabolic syndrome is 40% (20/50) among cases and 10% in control and it is statistically significant (p=0.001). The prevalence of MBS correlates well with the study of Dokras et al (47.3%), Dey et al (42%) and Glueck et al (43-46%). PCOS is responsible for prevalence of metabolic syndrome.^{7,8,13}

Use of both insulin sensitizers in present study reflects change in pathology in PCOS and causes change in symptoms, but weight loss has been emphasized in its management.^{18,19}

Resumption of menstrual abnormalities was noted in 61% of women with PCOS on myoinositol treatment; whereas the same effect was noted only in 26% by metformin treatment which was not clinically significant.

The pregnancy rate in infertile women treated with myoinositol was 50% without any use of additional ovulating agents which proves the good quality of oocytes and this fact was also noted by other studies.^{20,21} Metformin required additional ovulating agent clomiphene citrate for pregnancy in 7 out of 11 patients, so the actual pregnancy rate in this group cannot be ascertained properly. With myoinositol treatment the secondary outcome measures like weight, BMI, LH/FSH ratio and fasting insulin were reduced significantly, whereas

metformin has no significant effect on fasting insulin and LH/FSH hormone ratio which proves the superiority of myoinositol over metformin.

Myoinositol works at the ovarian level and causes change in hormonal milieu that improves the oocyte quality and better efficacy by combination of myo-inositol (MI) and D-chiro inositol (DCI) at the ratio of 40:1.²²

CONCLUSION

The prevalence of metabolic syndrome was 40% in the studied PCOS women.

There is a strong positive correlation between prevalence of MBS with BMI of PCOS women. Hyperinsulinemia has a critical link between PCOS and MBS. The waist circumference of ≥ 88 cm is the powerful predictor for prevalence of MBS amongst PCOS women.

Myoinositol produces significant improvement of symptom profile and hormonal milieu which improves oocyte quality and causes monofollicular recruitment that reduces the risk of side effects.

Myoinositol shows more favourable response in comparison to metformin in PCOS women. A prospective multicentre study with bigger sample size and longer follow-up is essential to establish the accurate result.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Modak R, Biswas DK, Pal A, Mandal TK. Prevalence and predictors of metabolic syndrome with comparison of myoinositol and metformin in PCOS women. *Int J Reprod Contracept Obstet Gynecol* 2019;8:570-5.