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A Comparative Study of Myo-Inositol versus Metformin in Women with Polycystic Ovary Syndrome

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ABSTRACT

To compare the efficacy of Myo-inositol versus Metformin on clinical, hormonal and metabolic profile while treating women with Polycystic Ovary Syndrome. Compared with Metformin, Myo-inositol significantly reduced serum fasting insulin levels and HOMA-IR (p-value <0.05). 65 % of patients in the Metformin group had side-effects, mainly gastrointestinal disturbances, whereas only 12% in Myo-inositol had side effects. Owing to better therapeutic efficacy, safety and tolerability profile, the observations of the present study justify the use of Myo-inositol as a safe, effective alternative and a new addition in the armamentarium of PCOS treatment.

Keywords:Myo-inositol ,diabetes mellitus, dyslipidemia, metabolic syndrome) and psychological features

1.INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common metabolic-endocrine disorders in women of reproductive age group, first described as a clinical entity by Stein and Leventhal 1 in 1935 and since then this disease has been recognized as a 'gynaecological curiosity with multi- system endocrinopathy' 2 . The cardinal features of this condition are hyperandrogenism (either clinical or biochemical), chronic anovulation, and polycystic o varies.According to World Health Organisation (WHO), about 116 million women (3.4%) have been affected by PCOS worldwide in 20123 . It has a significant and wide spectrum of clinical implications including reproductive (menstrual dysfunction, hirsutism, infertility), metabolic (insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, dyslipidemia, metabolic syndrome) and psychological features (anxiety, depression, negative body image, worsened quality of life) 4 . The condition affects several aspects of

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a woman's health right through menarche to well past her reproductive years.

In 2003, the Rotterdam European Society for Human Reproduction/ American Society of Reproductive Medicine (ESHRE/ASRM) consensus proposed that the diagnosis of PCOS include any two of the following three criteria viz. oligo- and/or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound; other etiologies must be excluded.Environmental and genetic factors have a significant role in the development of PCOS 5 . The pathophysiology of PCOS involves primary defects in three compartments namel y, the hypothalamic-pituitary ovarian axis, insulin secretion and action, and ovarian function. Insulin Resistance is a major driver of the pathogenesis of PCOS, which is present in approximately 50-75%6 , 7 , 8 of PCOS patients. Insulin resistance is postulated to be caused by defects in the insulin receptor and post receptor components of the insulin signalling pathway 9 , 10 . This results in modulation of activity of P450c17, which is the main regulatory enzyme in androgen biosynthesis, thus augmenting the ovarian and adrenal steroidogenesis causing hyperandrogenism. Hyperinsulinemia also causes abnormal functioning of hypothalamic - pituitary

ovarian axis leading to increased hypothalamic GnRH pulse frequency, which in turn results in an increase in the LH/FSH ratio in PCOS women11 .The management approach for PCOS women must be individualized to address the symptom burden while minimizing her risks and long-term clinical consequences through proper management and timely intervention with risk reduction strategies. Lifestyle modification and weight loss are the first-line of management.To combat insulin resistance in PCOS, Metformin, an oral biguanide, a time-tested drug, has been used since long, as a hepato-selective insulin sensitizer, in a dose of 500mg TDS with a success rate of 20 to 96% 12 - 18 . Metformin decreases hepatic gluconeogenesis, intestinal glucose uptake, increases peripheral insulin sensitivity, and inhibits lipolysis. It involves activation of adenosine monophosphate-activated protein kinase pathway in the liver and skeletal muscle. But, it is frequently associated with adverse effects such as nausea, vomiting, abdominal cramps and diarrhoea.

Myo-inositol (MI) is an upcoming, interesting molecule studied in the management of PCOS. It is found widely in nature and are second messengers , responsible for insulin mediated intracellular glucose transport, by augmenting the translocation of GLUT 4 to the cell membrane, and also involved in FSH signalling. A deficiency of inositols has been postulated as a key factor in the pathogenesis of insulin resistance in PCOS. An increased urinary excretion of inositol has also been observed in patients of PCOS thus leading to its deficiency19 . This opened up a new

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clinical interest on Myo- inositol, as a potential insulin sensitizing agent , and limited studies are available in India. As both Myo-inositol and Metformin have different mechanisms of action in improving insulin resistance, the purpose of this study is to evaluate the safe and effective options in the treatment of PCOS.

2.MATERIALS AND METHODS

STUDY DESIGN:

Comparative clinical study

STUDY CENTRE:

Out-patient department, Department of Obstetrics and Gynaecology, Sree Balaji Medical College and Hospital, Chromepet, Chennai – 600044.

STUDY PERIOD:

The study was carried out from August 2017 – February 2019 (18 months).

STUDY DURATION:

24 weeks treatment period per patient.

STUDY POPULATION:

Women in reproductive age group, both adolescents and adults, attending Gynaecology out-patient clinic of the hospital with menstrual irregularity (oligomenorrhea / amenorrhea), obesity, infertility with or without clinical evidence of hyperandrogenism were screened and diagnosed as having Polycystic ovary syndrome according to Rotterdamscriteria. The diagnosis of PCOS was made basedon atleast two of the three majorcriteria:

1. Oligo / anovulation (>35 days cycle or < 8 cycles of spontaneous menstrual period peryear)
2. Hyperandrogenism

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- Clinical :acne, hirsutism{modified FerrimanGallwayscore(mFG) ≥8} or androgenicalopecia
- Biochemical: raised Free Androgen Index(FAI) or free testosterone.

Polycystic appearing ovaries (assessed by ultrasonography, described as an ovarian volume of more than 10mL 3 and/or more than 12 follicles measuring between 2 and 9 mm in size in at least one ovary, excluding other etiologies having similar presentation.

SAMPLE SIZE:

Total 200 patients

INCLUSION CRITERIA:

Women of age group 18 -40 years, diagnosed with PCOS, as defined by the Rotterdam Criteria, who are willing to participate and give written informed consent, and who are able to comply with study procedures.

EXCLUSION CRITERIA:

1. Patients already on other drug treatment for PCOS (like oral contraceptivepills)
2. Patients with clinically significant cardiac, pulmonary, renal, hepatic, neurological, psychiatric illnessand malignantdisease.
3. Hyperprolactinemia
4. Adrenal disorders like Congenital AdrenalHyperplasia
5. Thyroiddisorders
6. Pregnant / Lactatingwomen
7. Established type 1 or type 2 diabetesmellitus
8. Known hypersensitivity to Myo-inositol /Metformin

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STUDY MEDICATION:

- Group A - Tab. Myo-inositol 1 gBD
- Group B - Tab. Metformin 500mgTDS

STUDY PROCEDURE:

The study was conducted after obtaining permission from the Institutional Ethics Committee (IEC). Women with PCOS attending Gynaecology OPD, were explained about the study purpose and procedures. Written informed consent was

obtained from the patients who were willing to participatein

thestudy.

STATISTICAL ANALYSIS:

The obtained data was analyzed statistically using SPSS software version 21. The results were tabulated and values were presented as mean (+ or -) and Standard Deviation (SD). Student's paired 't' test p value of < 0.05 was considered to be statistically significant.

1. RESULTS

A total of 200 patients were enrolled in the study, and allocated to either of the two treatment groups, by simple randomization. Patients in Group A received Tab. Myo-inositol 1 gram BD while patients in Group B received Tab. Metformin 500mg TDS for 24 weeks. Out of 200 patients enrolled in the study, 100 were allocated to Group A and 100 allocated to Group B.In Group A, 8 patients conceived during the treatment and2 patients were lost in follow-up. In Group B, 6 patients conceived during the treatment and 4 patients were lost in follow-up, and dropped out from the study. Remaining 90 patients in either group completed the treatment successfully.

The age distribution of the study population in Group A and B is shown in Table 5. It is significant from the above table that in both the groups, the majority of the subjects were between 21 - 30 years of age. There was no statistically significant difference found in age between the two groups. (paired t test applied, p-value- 0.995).

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TABLE 1: AGE DISTRIBUTION

Age (in years)	Group A Myoinositol	Percentage %	Group B Metformin	Percentage %	p Value
< 20	20	21	21	24	0.995
21 – 30	46	51	50	56	
31 – 40	24	28	19	20	
TOTAL	**90**	**100**	**90**	**100**	

The mean age of subjects was 26.70±6.78 and 25.88±6.24 in Group A and Group B respectively, as shown in Table 6. There was no statistically significant difference between the groups.(p-value-0.784).

FIGURE 1: MARITAL STATUS

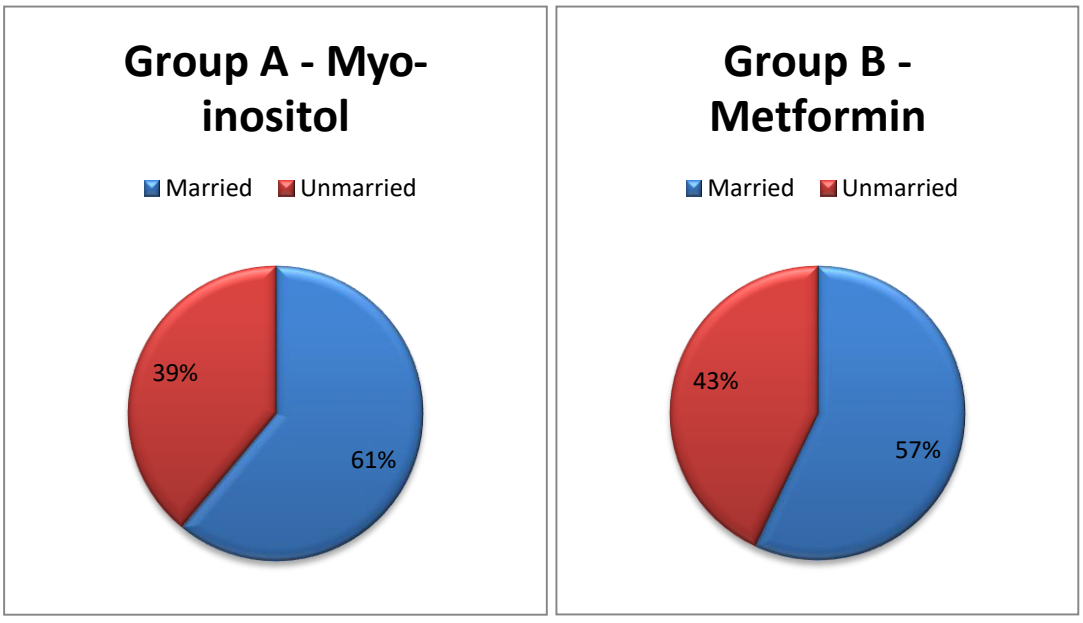

TABLE 2 : SOCIO ECONOMIC STATUS

Socio economic status	GROUP A Myoinositol	%	GROUPB Metformin	%

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Class I (Upper)	10	11	11	12
Class II(Upper Middle)	11	12	9	10
Class III (Lower Middle)	19	21	24	28
Class IV (Upper Lower)	37	41	34	37
ClassV (Lower)	13	15	12	13
TOTAL	**90**	**100**	**90**	**100**

Among the cases, in Group A (Myo-inositol)socio economic status was classified from class I to V, according toModified Kuppuswamy Scale, with maximum number (41%) in class IV, followed by class III (21%) and remaining 15%, 12 % & 11 % in class V, class II & class I respectively and th e same in Group B (Metformin) was classified as from class I to V with maximum number (37%) in class IV, followed by class III (28%) and the remaining 13%, 12 % & 10 % in class V, class II & class I respectively.

There was no statistically significant difference found in age between the two groups. (paired t test applied, p value ≥ 0.05).

TABLE 3 –INFERTILITY AMONG MARRIEDWOMEN

INFERTILITY	**Group A-Myoinositol**	**Group B-Metformin**	**p-value**
Total number of married women	63	57	0.652
Infertility	34	32	
Percentage %	54%	57%	

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Among the total cases, 54 % of Group A & 57 % of Group B had infertility among married women. However there was no statistical significance between the groups. (P > 0.05).

TABLE 4: ACNE AND HIRSUTISM

Cutaneous Manifestations of Hyperandrogenism	Group A - Myoinositol		Group B - Metformin		p value
	No. of cases	%	No. of cases	%	
Acne	25	28	29	32	0.096
Hirsutism	41	45	44	49	0.874

TABLE 5:MEAN WEIGHT(kg)

GROUP A - Myoinositol			GROUP B - Metformin			p-value
Pre-treatment (Mean±SD)	Post-treatment (Mean±SD)	p-value	Pre-treatment (Mean±SD)	Post-treatment (Mean±SD)	P value	
64.87 ± 8.99	60.46 ± 4.85	0.000	62.15 ± 7.54	55.54 ± 5.24	0.000	0.000

With respect to mean weight, Group A had a mean of 64.87 pre-treatment and the same was found as 60.46 post-treatment. Group B had a mean of 62.15 pre-treatment and the same was found as 55.54 at the 24th week(post-treatment).

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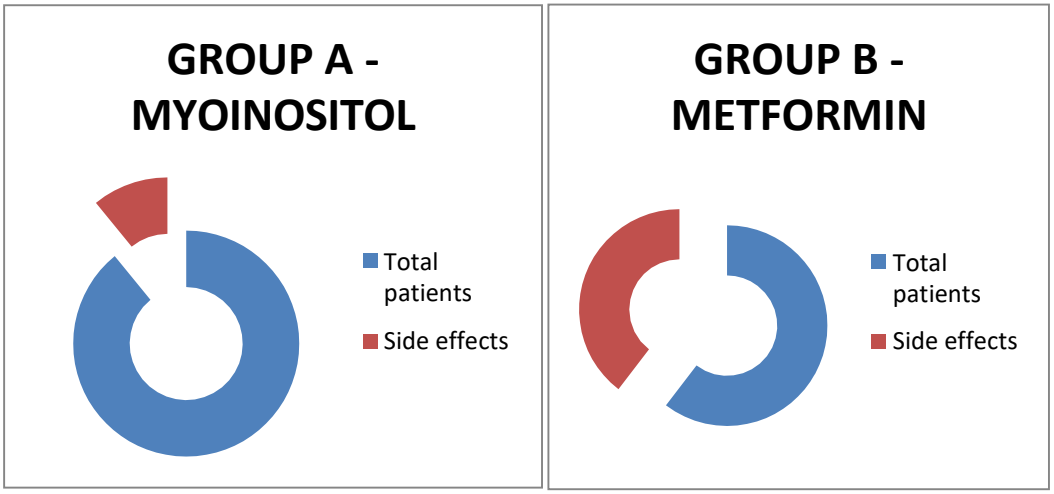
TABLE 6– LH/ FSH ratio

GROUPS	LH/FSH				P value
	Pre-Treatment		Post-Treatment		
	Mean	S.D.	Mean	S.D.	
GROUP A (Myo-inositol)	2.34	0.34	1.91	0.32	0.000
GROUP B (Metformin)	2.35	0.37	2.06	0.33	0.000
p-value	0.841				

Table6 shows mean LH/FSH ratio in both groups at baseline and at the end of 24 weeks. Statistical analysis within the groups showed a significant decrease in the LH/FSH ratio at the end of 24 weeks ($p < 0.05$). On comparing both groups, no statistical difference was observed between the groups (p - 0.841).

FIGURE 2: ADVERSE DRUG REACTIONS



Among the study population, in Group A, 4 patients had nausea, 3 had generalized weakness, 2 had diarrhoea and 3 patients had abdominal pain. In Group B, 25 patients had nausea, 11 had generalized weakness, 5 had diarrhoea and 8 atients had abdominal pain.

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3. DISCUSSION

PCOS is one of the most common hormonal and metabolic abnormality affecting reproductive-aged women (affecting approximately 10%) with key features of menstrual irregularity, elevated androgens and polycystic appearing ovaries. Approximately 50 -75% of PCOS women exhibit insulin resistance, which is defined as the inability to fulfil the metabolic demands of peripheral tissues in spite of secretion of increased amount of insulin in the circulation. One of the most surprising features of insulin resistant PCOS is that when all other organs are insulin resistant, ovaries remain hyper-responsive. Involvement of IGF-1 and an intrinsic ovarian and adrenal enzyme P450C17 α has been suggested as possible avenues through which hyperinsulinemia, acts synergistically with LH to enhance the androgen production from the theca cells.20 Hence, insulin acts as a 'co-gonadotropin'. In addition, it is able to reduce circulating levels of SHBG, leading to increased levels of free testosterone. Considered altogether, this evidence has paved way for the use of insulin sensitizing drugs to reduce the severity of PCOS.Metformin, a hepato-selective insulin sensitizer, is considered one of the first line approaches to insulin resistance, and it is a time-tested drug for combating obesity, hormonal and metabolic derangements in PCOS. On the other hand, Myo-inositol, a non-hormonal natural supplement , plays a crucial role at ovarian level promoting glucose uptake, and FSH signalling, whereas DCI mediates the insulin- mediated androgen production. By rescuing the ovarian response to endogenous gonadotropins, MI reduces hyperandrogenemia and re-establishes menstrual cycle cyclicity and ovulation, increasing the chance of a spontaneous pregnancy.21

In the present study, patients in the two groups are adequately matched with respect to age, marital status, socioeconomic status, symptom profile like menstrual dysfunction, acne and hirsutism, and anthropometric assessments like weight and body mass index ($p>0.05$).In the present study, 23.5% of the infertile patients in Myo-inositol group and 18.7% of them in Metformin group achieved spontaneous conception. Similar findings were observed in a study conducted by Raffone, E., et al (2010) 14 , in which 120 infertility patients with PCOS were treated with Metformin 1500 mg/day, or 4 g Myo-inositol plus 400 µg folicacid continuously. If no pregnancy occurred, r -FSH (37.5 units/day) was added to the treatment for a maximum of three attempts. The total pregnancy rate was 36 .6% and 48.4% in Metformin and Myo-inositol groups respectively.22

A study done by Papaleo, E., et al (2009) 56 demonstrated that in patients undergoing

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ICSI, the total r -FSH units and number of days of stimulation and peak E 2 levels at hCGadministration(decreased risk of hyperstimulation), mean number of germinal vesicles and degenerated oocytes at ovum pick-up without compromising total number of retrieved oocytes were significantly lower on treatment with Myo- inositol, with an increased trend of oocytes in metaphase II. This signifies the role of Myo-inositol on ovulation induction, in the near future.23 In the present study, there was a statistically significant reduction in LH levels and LH/FSH ratio in both the groups (p value <0.05). No significant difference was found in FSH levels in both the groups. Both Myo-inositol and Metformin led to significant reduction in total testosterone (pvalue<0.000) in the present study. But on comparing thedrugs, no statistical difference was noted. Similar results are noted in the following studies:A randomized controlled trial conducted by Jamilian, M., et al. (2017) 58 among 60 PCOS patients, receiving either Myo-inositol or Metformin for 12 weeks, concluded that, compared with Metformin, Myo-inositol intake significantly decreased serum total testosterone (P=.03).

Another study conducted by Fruzzetti, F., et al. (2017) 63 in which 50 PCOS women with insulin resistance (HOMA- IR>2.5) or hyperinsulinemia were randomized to receive Metformin 1500 mg/day or Myo-inositol 4 g/day) for 6 months. 24,25 They concluded that both the groups increased insulin sensitivity, lowered BMI and improved menstrual cycle in about 50% of the women, without significant differences between the two groups. 26 In the present study, there was a significant reduction in ovarian volume post-treatment with both Myo-inositol (p- value-0.001) and Metformin (p-value-0.041). No statistical difference observed between the drugs. A study done by FarimaniSanonee et al 64 showed a significant reduction in mean ovarian volume (11.70±4.31ml Vs 8.27±3.71ml; p value=0.001) after three months of treatment with Metformin.

In the present study, among the total cases, 12 % of patients in Myo-inositol group and 65 % of patients in the Metformin group had side-effects, mainly generalised weakness and other gastrointestinal disturbances. Similar findings are noted in a study done by Carlomagno G et al 52 , in which only the highest dose (12 g/day) of Myo-inositol induced mild gastrointestinal side effects such as nausea, flatulence and diarrhoea. Thus, Myo-inositol is a safe and secure drug with better patient compliance, which in turn leads to better therapeutic outcomes in PCOS patients.27

5.CONCLUSION

"PCOS affects over 7 million people. That's more than the number of people diagnosed with breast cancer, rheumatoid arthritis, multiple sclerosis, and lupus combined." Louise Chang,

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MD.Polycystic Ovary Syndrome is a multifaceted disorder involving a spectrum of genetic, hormonal, metabolic and reproductive complications, affecting the adolescent girls and women of childbearing age. Also known as the 'Perfect Hormonal Storm', PCOS is one of the leading causes of female infertility. Insulin resistance is now recognized as having a central role in the pathophysiology of PCOS.

Over 50% of women with PCOS are going undiagnosed. Hence, the first important step is to create proper awareness which paves way for early detection of PCOS, and also helps the affected women to overcome their symptoms, by encouraging lifestyle changes, and judicious medical intervention for a successful reproductive career in child bearing age, and more importantly for reducing the far reaching consequences of PCOS like obesity, impaired glucosetolerance, type II diabetes mellitus, dyslipidemia, cardiovascular health risk, metabolic syndrome, non-alcoholic fatty liver disease, psychological disorders and cancer.

Myo-inositol, a second messenger regulating many hormones such as Insulin and FSH, positively affects different pathways at both ovarian and non-ovarian level, could fruitfully improve different physiological aspects of PCOS. In the present study, using a comprehensive clinical, endocrinological and metabolic assessment, it has been shown that both Myo-inositol and Metformin resulted in significant weight loss, regularisation of menses and improvement in endocrinological and metabolic parameters. But, th e cost of treatment with Myo-inositol 2g/day for 3 -6 months is one of the major constraints. Owing to better therapeutic efficacy, safety and tolerability profile, the observations of the present study justify the use of Myo-inositol as a safe, effective alternative and a new addition in the armamentarium of PCOS treatment.

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

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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BIBLIOGRAPHY

1) Stein IF and Leventhal ML.Amenorrhoea associatedwith bilateral polycystic ovaries. Am. J Obstet. Gynecol1935; 29:181-9.
2) Homburg R Polycystic ovary syndrome from gynaecological curiosity to multisystem endocrinopathy. Br J ObstetGynecol1990;97:695-9
3) A.M. Kabel. Polycystic ovarian syndrome: insights into pathogenesis, diagnosis, prognosis, pharmacological and non-pharmacologicaltreatment.Pharmacol. Rep., 1 (103) (2016), pp.E1-E5.
4) TeedeH, DeeksA, MoranL. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifesationsthat impactsonhealth across the lifespan. BMC Med. 2010 Jun 30;8:41. doi: 10.1186/1741-7015-8-41. PubMed PMID: 20591140; PubMed Central PMCID:PMC2909929.
5) Kovacs N. polycystic ovary syndrome. Second edition, Cambridge University: 2013,pp.13.
6) Carmina E, Koyama T, Chang L, Stanczyk FZ, Lobo RA, Doesethnicity influence the prevalenceof adrenalhyperandrogenism and insulin resistance in polycystic ovary syndrome? Am J ObstetGynecol 167:1807, 1992.
7) DunaifA, Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis, EndocrRev 18:774,1997.
8) LegroRS, A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome, J Clin Endocrinol Metab83:2694,1998.
9) Rojas J, Chavez M, OlivarL, Rojas M, MorilloJ,MejiasJ, et al. Polycystic ovary syndrome, insulin resistance and obesity: navigating the pathophysiologic labyrinth. International Journal of Reproductive Medicine. 2014;719050.doi:1155/2014/719050.
10) BrettenhalerN, De GeyterC, Huber PR, Keller U. Effect of insulin sensitizer pioglitazone onIR, hyperandrogenism and ovulatory dysfunction in women with PCOS. Journal of Clinical Endocrinology and Metabolism 2004; 89(8):3835 –3840.
11) AlemzadehR, Kichler J, Calhoun M. Spectrum of metabolic dysfunction in relationship with hyperandrogenemia in obese adolescent girlswith polycystic ovary syndrome. European Journal of Endocrinology Jun 2010;162(6):1093-1099.
12) Nazari T, BayatR, HamediM.Metformin therapyin girls with polycystic ovary syndrome: a selfcontrolledclinical trial. Archives Iranian Med. 2007;10(2):176-81
13) Ashrafi M, ZafaraniF, BaghestaniAR. Effects of metformin on ovulation and pregnancy rate inwomen with clomiphene resistant polycystic ovary syndrome. Int JFertilSteril.2007;1(1):39
14) RaffoneE, Rizzo P, BenedettoV.Insulinsensitiseragents alone and in co-

treatmentwith r-FSH for ovulation induction in PCOS women. GynecolEndocrinol.2010;26(4):275-80.

15) Le Donne M, Alibrandi A, GiarrussoR, LoMI, MuracaU. Diet, metformin and inositol in overweight and obese women with polycystic ovary syndrome: effects on body composition. Minerva Ginecol.2012;64(1):23 -9.
16) AngikR, JajooSS, Hariharan C, ChimoteA. A comparative study of metabolic and hormonal effects of myoinositol vs. metformin in women with polycysticovary syndrome: A randomised controlled trial. Int J ReprodContracept ObstetGynecol.2017;4(1):189 -4.
17) AwalekarJ, AwalekarC, Jadhav M, ChivateCG, Patwardhan MH. Effect ofmetforminand myoinositoland lifestyle modification in patients of PCOD. Int J Biomed Res 2015;6(09);698-704
18) ChiraniaK, MisraS, Behera S. Arandomisedclinicaltrial comparing myoinositol and metformin in PCOS .Int J ReprodContracept ObstetGynecol.2017;6(5):1814 -20.
19) Gill H, Tiwari P, DabadghaoP. Prevalence of polycystic ovary syndrome in young women from North India: A Community-based study.IndianJournalof Endocrinology and Metabolism 2012;16(Suppl 2):S389- S392.
20) Goodman, Gillman. The pharmacological basis of therapeutics. twelfth edition, 2011; Chapter5: 1258.
21) Katzung, G.Mastersb.TrevorJ.Basic, Clinical pharmacology. 12th edition. Chapter, 2012;41: 757.
22) MacielGA, Soares Junior JM, Alves da Motta EL, Abi Haidar M,de Lima GR &BaracatEC. Nonobese women with polycystic ovary syndrome respond better than obese women to treatment with metformin. Fertility and Sterility, 2004;81:355–360.
23) Fleming R, Hopkinson ZE, Wallace AM, GreerIA&Sattar N. Ovarian function and metabolic factorsin womenwith oligomenorrhea treated with metformin in a randomized doubleblindplacebo-controlledtrial. Journal of Clinical Endocrinology and Metabolism,2002; 87:569–574.
24) Jonathan M L, Ingrid H K F, Robert J N. Metformin in polycystic ovary syndrome: systematic review and meta- analysis. BMJ, Oct 2003; 327(7421):951.
25) VaijinathBiradar, Sangeeta Tengli. “Myoinositol in PCOS”. Journal of Evidence based Medicine and Healthcare, December 15, 2014; Vol.1,Page:1927 -1936.
26) Artini, P. G., et al. (2013). "Endocrine andclinical effects of myo-inositol administrationinpolycysticovary syndrome. A randomized study."GynecolEndocrinol 29(4): 375-379.
27) FarimaniSanoee, M., et al. (2011). "Metformin therapy decreases hyperandrogenism and ovarian volumein women with polycystic ovary syndrome." Iran J MedSci36(2): 90-95