Effect of metformin & myoinositol & life style modification in patients of polycystic ovarian disease (PCOD)

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Abstract
Polycystic ovarian disease (PCOD) is common endocrine disorder. Majority of young females are affected. Insulin resistance along with dysfunction of hypothalamo pituitary adrenal axis is a key etiological factor in development of all manifestations of PCOD. They present with irregular menses, infertility, obesity, Hirsutism, Acanthosis Nigricans etc. Metformin, Myoinositol & life style modification are widely accepted treatment modalities. Data suggests variable responses to these treatments. So we aimed to study efficacy of each treatment modality separately in PCOS. Here cases are diagnosed by using Rotterdam’s criteria. We recruited approx 30 cases for each group. BMI, Menstrual irregularity, infertility, Hirsutism, Acanthosis Nigricans, acne were common presenting features. Hormonal & biochemical profile was studied S.LH (Luteinizing Hormone), FSH (Follicle stimulating hormone), Serum. Prolactin levels, Serum Insulin levels. Weight loss, menstrual regularity, LH/FSH Ratio, HOMA Index were studied initially & compared all parameters after 3 months of treatment. In our study Metformin group (n=35), Myoinositol group(n=32) & for Life style modification(n=35).Our study Metformin group BMI reduced from mean 29.64 to 27.13 after 3 months Metformin treatment which is highly significant(p<0.0000). LH/FSH ratio was mean 2.56, dropped to 1.70,(p<0.000) after treatment, which is significant. Homa index values before treatment were mean 25.85, & after treatment it was 15.21(p<0.000) highly significant. Hyperprolactinemia corrected from Mean 24.11 to 16.92 to 6.27 (p<0.004) found to be statistically significant. In Myoinositol group BMI was mean 26.71, after treatment it became25.6. In Life style modification group BMI before was mean 26.55 to 25.77(p). LH/FSH ratio was 2.mean & later 3 months it became 2.10,(p=001) initially, after 3 months it was-.HOMA index in this group was14.73after 3 months it was13.35. The present study gives us idea about efficacy of different modalities of treatment in PCOD cases & will be useful in patient treatment schedules.

Keywords: Hyperinsulinemia, Metformin, Myoinositol, Life style modification, BMI (Body Mass Index), LH/FSH-Luteinizing hormone & Follicle stimulating hormone ratio, HOMA index-Homeostatic model assessment

1. Introduction
Nowadays Poly Cystic Ovarian Disease (PCOD) is commonest endocrine disorder in young females. It is characterised by insulin resistance & is strongly implicated in its aetiology.

"Polycystic ovari syndrome: a complex conditions with psychological, reproductive and metabolic manifestations those impacts on health across the lifespan".[5] In 2003 a consensus workshop sponsored by ESHRE/ASRM in Rotterdam indicated PCOS to be present if any 2 out of 3 criteria are met [2,7,8] it also includes many women without androgen excess too.

1) Oligoovulation and/or anovulation
2) Excess androgen activity
3) Polycystic ovaries (by ultrasound)
4) Other entities are excluded that would cause these.[5,8]
Insulin resistance & obesity is observed in majority of PCOD patients. Elevated insulin levels cause abnormal functioning of hypothalamic-pituitary-ovarian axis that lead to PCOS. Women with PCOS experience an increased frequency of hypothalamic GnRH pulses, which in turn results in an increase in the LH/FSH ratio[8].

Insulin resistance is main causative factor for all these consequences & morbidity. Failure of the target cells to respond to normal or ordinary levels of insulin is regarded as insulin resistance irrespective of the body mass index (BMI). Hyperinsulinemia due to insulin resistance occurs in approximately 80% of PCOS women central obesity & 30%–40% of lean PCOS women. Measurement of the fasting insulin concentration [10] is an easy marker to obtain, and values equal to 20 or higher indicate the presence of insulin resistance. Hyperinsulinemia is the main causative factor in PCOD women both obese & lean[4,5] & cause hyperandrogenism. Insulin directly promotes ovarian steroidogenesis, and inhibits liver release of the sex hormone binding globulin (SHBG) and production of insulin-like growth factor binding protein 1 (IGFBP-1). Increased concentrations of IGF-1 additionally promote ovarian release of androgens [26].

1.1 Insulin Resistance

We have used HOMA index as a marker of insulin resistance, based on measurements of fasting glucose and insulin levels, is the homeostatic model assessment (HOMA-IR). Resistance to insulin is diagnosed at HOMA-IR levels ≥3.8[26].

Insulin resistance can manifest as follows:

1) Insulin resistance/Type II diabetes [1,4].
2) Weight gain [1,3,14]
3) High blood pressure, in obese and/or during pregnancy.[11]
4) Cardiovascular disease-two fold increased risk of arterial disease in PCOS patients as compared to women without PCOS [7,14]
5) Strokes [2,3]
6) Miscarriage[6,7]
7) Sleep apnoea, in obese[7,14]
8) Non-alcoholic fatty liver disease, in obese[14,15]
9) Acanthosis nigricans (patches of darkened skin under the arms, in the groin area, on the back of the neck [15].

Adipose tissue enzyme, aromatase, converts androstenedione to estrone and testosterone to estradiol. The excess of adipose tissue in obese led excess androgen formation, which are responsible for hirsutism and virilization. Excess estrogens, inhibits FSH via negative feedback [15]. It is been treated with various treatment modalities successfully.

Metformin, Myo-inositol, Life style modifications are most frequently used treatment modalities in PCOD females.

Metformin is a hepato-selective insulin sensitiser. It has beneficial properties of weight loss, lipid reduction and modulator of endothelial function. It is anatherostatic agent and also improves ovarian function in insulin-resistant women. It does not cause hyperinsulinemia or hypoglycaemia[7]. Beneficial effects of metformin on reducing androgen levels and restoring ovulation in women with polycystic ovary syndrome (PCOS) have been published [6,9]. As insulin resistance as a predictor of diabetes, hypertension and coronary artery disease, metformin is increasingly prescribed to insulin-resistant women with PCOS[2].

Myo-inositol (MYO) and D-chiro- inositol (DCI); both stereo-isomers were used, as insulin sensitizer drugs, in the treatment of PCOS treatments [19,23]. Inositol belongs to the vitamin B complex. Epimerization of the six hydroxyl groups of inositol leads to the formation of up to nine stereo-isomers, including Human adults consume approximately 1 g of inositol (mainly MYO) per day in different biochemical forms [18].

Inositol phosphoglycans (IPGs) activate enzymes that control glucose metabolism [16,17]. Defect in the IPGs, second messenger can cause impaired insulin metabolism [14,15]. In PCOS women, a defect in tissue availability or altered metabolism of IPGs (inositol) mediators may contribute to insulin resistance [18]. Circulating free MYO is taken up by most tissues by a membrane-associated sodium-dependent inositol co-transporter; inositol uptake is inhibited by glucose [24]. In particular, it was shown that MYO had 10 times more affinity for the transporter compared to DCI [25].

PCOS is associated with selective increase in urinary clearance of D-chiro-inositol (DCI) & impaired DCI inositol phosphoglycan release in response to insulin. That means defect in tissue availability or utilization of DCI in PCOs that may contribute to insulin resistance.

DCI increases the action of insulin in patients of PCOS, thereby improving ovulatory function & decreasing serum androgen concentration, blood pressure & plasma triglyceride concentration. Women with PCOS have Insulin Resistance with hyperinsulinemia because of deficiency of DCI containing phosphoglycan that mediates action of insulin [3,4].

Elevated concentrations of MYO in human follicular fluid play a role in follicular maturity and provide a marker of good-quality oocytes[4,6]. Previous studies have demonstrated that MYO is capable of restoring spontaneous ovarian activity, and
consequently fertility, in most patients with PCOS [6].

Lifestyle modification programmes include behavioural management and dietary and exercise interventions. These are found helpful in reducing the risk of diabetes and the metabolic syndrome. Also it is successful in improving fertility outcomes in PCOS [9,10]. However, the literature on effective diet and exercise programmes for PCOS has been sparse [13]. A scientific review in 2013 found similar decreases in weight and body composition and improvements in pregnancy rate, menstrual regularity, ovulation, hyperandrogenism, insulin resistance, lipids, occur with weight loss independent of diet composition [14,15]. Low GI diet, containing fruit, vegetables, and whole-grain sources, has resulted in greater menstrual regularity than a macronutrient-matched healthy diet [8,13].

Metformin, Myoinositol & Life style modification are main treatment modalities for PCOS accepted worldwide & proved beneficial to varying extent. However its very sparse

2. Methods

2.1 Study Design, Size & Duration

This is comparative observational was study done at Bharati Vidyapeeth Deemed University Medical College & Hospital, Sangli & Dr. Patwardhan’s Endocrinology & Research Centre Miraj. It was carried out from June 2013 to June 2015. In cases of PCOD effect of Metformin, Myoinositol & Life style modification is observed.

We recruited approx 30 patients of PCOD group. Each diagnosed by using to Rotterdam criteria for each group.

2.1 Criteria of Exclusion

1. Cushings syndrome
2. Thyroid disorders
3. Pituitary tumours
4. Diabetes Mellitus
A. Written consent is taken before starting examination.
   • History & Clinical examination is done.
Following points were considered for comparison.
1. Height in metre, weight in Kg & Body Mass Index (BMI) is calculated.
2. Menstrual irregularities are noted as amenorrhoea, oligomenorrhoea & irregular cycles.
3. Infertility.

B. Following investigations were done-
1. LH (Luteinizng Hormone).
2. FSH (Follicle stimulating hormone).
3. Serum. Prolactin levels-
4. Serum Insulin levels-
C. Following parameters were studied for comparison
1. BMI reduction-
2. LH/FSH Ratio-
3. HOMA Index-homeostatic model assessment (HOMA): method used to quantify IR & beta-cell function. It also predicts cardiometabolic risk .Calculated by using formula HOMA-IR = [Glucose] x [Insulin] / 405 (Glucose in mg/dl)

Following Treatment schedules are advised to particular groups & seen that they stick to schedule.

Metformin Group: We have included 35 diagnosed cases of PCOD in this group.(Rotterdam’s criteria). Both obese & thin are included. Tab Metformin500mg TID was advised half hour before meals. All parameters of comparison given above repeated after 3 months.

Myoinositol Group: We have included 32 patients of PCOD in this group. Tab Myoinositol 2 gm BID along with Tab. Folic acid 5mg OD is advised to these patients. All parameters of comparison given above repeated after 3 months.

Life style modification group: 34 Patients of PCOD are included in this group. Diet & exercise guidelines were advised to each participant with the help of dietician & gym trainer.

Diet: Balanced diet comprising 50% carbohydrates, 20% proteins & 30% fat is prescribed. Fat intake was advised to have 10% saturated, 10% polysaturated & 10% monounsaturated fats. Daily protein intake of 0.8-1gm/kg bodyweight is advised.

Low calorie balanced diet inclusive of different food categories was maintained. Carbohydrates, proteins, fat, minerals, fruits & vegetables were advised appropriate proportions. The general rule of weight loss of 0.5-1Kg weekly. Deficit of 3000-7000 calories per week was essential for weight loss.

Basic dietary principle of dividing diet into several small meals during the day like, breakfast, lunch, dinner, 2-3 small meals in between.

After 3 months of treatment in each group all the parameters are observed & compared.
3. Results & Discussion

Table No. 1: Metformin Group

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
<th>T</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>pre BMI</td>
<td>29.64</td>
<td>3.49</td>
<td>0.59</td>
<td>9.49</td>
<td>0.000</td>
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<tr>
<td>post BMI</td>
<td>27.13</td>
<td>3.48</td>
<td>0.58</td>
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<tr>
<td>pre HOMA index</td>
<td>25.85</td>
<td>16.27</td>
<td>2.75</td>
<td>4.55</td>
<td>0.000</td>
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<tr>
<td>post HOMA index</td>
<td>15.21</td>
<td>13.69</td>
<td>2.31</td>
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<tr>
<td>Pre LH/ FSH</td>
<td>2.56</td>
<td>0.24</td>
<td>0.04</td>
<td>12.60</td>
<td>0.000</td>
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<tr>
<td>Post LH/ FSH</td>
<td>1.70</td>
<td>0.28</td>
<td>0.04</td>
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</table>

1. In our study In Metformin group n=35, before starting treatment BMI mean was 29.64, after 3 months treatment with Metformin it reduced to 27.13 (p=0.000) i.e. highly significant statistically.
2. HOMA index pre treatment was mean 25.85, reduced to 15.21 (p=0.000). i.e. highly significant statistically.
3. LH/ FSH ratio which suggests insulin resistance was mean 2.56 before starting treatment. It slashed down to 1.7 (p=0.000) i.e. highly significant statistically.

All these results suggest Metformin is very good treatment option in PCOD.

Table No. 2: Myoinositol Group

<table>
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<th>Std. Error Mean</th>
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<tr>
<td>pre BMI</td>
<td>25.40</td>
<td>6.53</td>
<td>1.15</td>
<td>2.77</td>
<td>0.009</td>
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<tr>
<td>post BMI</td>
<td>24.40</td>
<td>5.91</td>
<td>1.04</td>
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<tr>
<td>pre HOMA index</td>
<td>23.74</td>
<td>25.00</td>
<td>4.42</td>
<td>0.006</td>
<td>0.995</td>
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<td>post HOMA index</td>
<td>23.8</td>
<td>44.62</td>
<td>7.88</td>
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<tr>
<td>Pre LH/ FSH</td>
<td>2.32</td>
<td>0.29</td>
<td>0.05</td>
<td>3.78</td>
<td>0.001</td>
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<tr>
<td>Post LH/ FSH</td>
<td>2.10</td>
<td>0.43</td>
<td>0.077</td>
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</table>

1. In our study In Metformin group n=32, before starting treatment BMI mean was 25.40, after 3 months treatment with Myoinositol it reduced to 24.40 (p=0.009) i.e. highly significant statistically.
2. HOMA index pre treatment was mean 23.74, reduced to 23.8 (p=0.995). i.e. not significant statistically.
3. LH/ FSH ratio which suggests insulin resistance was mean 2.32 before starting treatment. It slashed down to 2.10 (p=0.001) i.e. highly significant statistically.

All these results suggest Myoinositol has been effective in reducing BMI & LH/ FSH ratio significantly. But there was no change in HOMA index. So Myoinositol can be good treatment option in PCOD.

Table No. 3: Life style Modification Group

<table>
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<th>Std. Error Mean</th>
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<th>p value</th>
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<tr>
<td>pre BMI</td>
<td>26.55</td>
<td>4.77</td>
<td>0.81</td>
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<td>0.000</td>
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<td>post BMI</td>
<td>25.77</td>
<td>4.45</td>
<td>0.76</td>
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<tr>
<td>pre HOMA index</td>
<td>13.87</td>
<td>8.26</td>
<td>1.41</td>
<td>-0.25</td>
<td>0.804</td>
</tr>
<tr>
<td>post HOMA index</td>
<td>14.70</td>
<td>16.74</td>
<td>2.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre LH/ FSH</td>
<td>2.15</td>
<td>0.53</td>
<td>0.09</td>
<td>1.89</td>
<td>0.067</td>
</tr>
<tr>
<td>Post LH/ FSH</td>
<td>2.00</td>
<td>0.29</td>
<td>0.05</td>
<td></td>
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</tr>
</tbody>
</table>

1. In our study In life style modification group n=35, before starting treatment BMI mean was 26.55, after 3 months intensive diet & exercise schedule it was reduced to 25.77 (p=0.000) i.e. highly significant statistically.
2. HOMA index pre treatment was mean 13.87, reduced to 14.7 (p=0.804), i.e. not significant statistically.
3. LH/ FSH ratio which suggests insulin resistance was mean 2.15 before starting treatment. It slashed down to 2.0 (p=0.067) i.e. not significant statistically.

All these results suggest Life Style modification has reduced BMI significantly. In other parameters it could not change, so we can say it can be good supportive treatment option in PCOD in addition to Metfomin or Myoinositol or both.
incidence of infertility due to PCOD per million was 375 patients (total 180). Of those, 140 appeared to respond well to clomiphene (78%) but 40 (22%) failed, requiring alternative therapy.

Jonathan et al have done meta-analysis showed Metformin has an effect in reducing fasting insulin concentrations & is effective in achieving ovulation in PCOD women, when compared Metformin with Placebo. Pregnancy rates were significant by treatment effect for metformin and clomiphene. This study did not show any effect on body mass index or waist: hip ratio. Metformin was associated with a higher incidence of nausea, vomiting, and other gastrointestinal disturbance [26]. Its choice as a first line agent seems justified. It should be used as an adjuvant to general lifestyle modification in patients of PCOD where all parameters were significantly reduced.

Table 4, explains after effect of each treatment modality. It suggests each parameter is significantly affected by Metformin.

4. Discussion

PCOD patients present with menstrual irregularities like amenorrhea, oligomenorrhea about half of them have infertility because of anovulation caused by because of hormonal dysfunction & insulin resistance. Hirsutism, acne, obesity, miscarriages, hypertension, Ischaemic Heart Disease, diabetes, sleep apnoea etc.

The population studies revealed, first, that overt and occult PCOD accounted for 90% of patients with oligomenorrhea and 37% with amenorrhea, or 73% with oligo or amenorrhea. Oligo or amenorrhea accounted for 21% of couples with infertility and the annual incidence was 247 patients per million of the general population. The annual incidence of infertility due to PCOD per million was 41 with overt PCOD and 139 with occult PCOD (total 180). Of those, 140 appeared to respond well to clomiphene (78%) but 40 (22%) failed, requiring alternative therapy.

Table 5: ANOVA for difference in pre operative and post operative

Table 4, explains comparative effect of each treatment in each parameter we studied modality. Differences of all parameters before & after intervention suggest that Metformin is effective treatment in PCOD where all parameters were significantly reduced.
improvements and not as a replacement for increased exercise and improved diet.

Costantino et al [19] recruited 42 patients treated with MYO showed there was no change in the fasting plasma insulin and glucose concentration. AUC, for both insulin and glucose, decreased during the oral glucose tolerance. There was no change in the fasting plasma insulin and glucose concentration. Ovulation was restored in 16 (69.5%) women treated with MYO group.

According to Gerl et al, The BMI decreased significantly in the MYO group (p = 0.04). No change was observed in the waist-to-hip ratio [17].

Raffone et al performed a study aiming to compare the effects of metformin and MYO on PCOS patients. Among the metformin group, 50% restored spontaneous ovulation activity; in these patients Pregnancy occurred spontaneously in 11 of these patients; Raffone et al showed that MYO slightly improves pregnancy rate compared to metformin; no side effects were reported [18].

The randomized, prospective, multicenter study conducted by Tang and colleagues [23] assessed whether lifestyle changes alone or in combination with metformin (an insulin sensitizer) are associated with superior endocrine, anthropometric, and menstrual cycle characteristics among PCOS women.

Patients in both groups showed similar improvements in their menstrual cyclicity [23] with 52.2% improvement in the metformin group and 58.1% in the placebo group. Significant weight loss was achieved in both groups. The loss was greater in the metformin group, but the difference was not significant. Androgen levels were reduced in the metformin group only. Glucose and insulin levels and insulin sensitivity did not change with either approach. Spontaneous pregnancy rates were similar in both groups.

This study showed that lifestyle management alone -- i.e., weight loss -- was as effective as lifestyle management in combination with metformin regarding the improvement of menstrual cyclicity among obese women with PCOS.

Studies have shown that lifestyle change resulting in weight loss reduced the risk of type 2 diabetes [24]. The same studies found lifestyle changes to be superior to metformin [25].

5. Conclusions
Metformin significantly improves insulin sensitivity in insulin resistant patients. It was associated with improvement in insulin sensitivity in HOMA-IR defined insulin resistant patients. Metformin did very well in all aspects we studied, so it can be used as first line therapy in PCOD.

Myoinositol did better in this study. Being physiological component It may be combined in treatment of PCOD with other treatment options.

Life style modification could change BMI significantly.

All PCOS women should be advised to follow healthy life style modification. Their chance to achieve a pregnancy will improve and the risks during pregnancy will be reduced. It reduces their long-term risks for diabetes, hypertension, dyslipidemia, and cardiovascular disease. It is essential for all primary care providers to identify patients of PCOS. These patients should undergo the appropriate tests and should be counselled & treated accordingly.

References
[8] Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS. A randomized, 48-week,


