INTRODUCTION
Polycystic ovarian syndrome (PCOS) is common in about 10% of females of reproductive age group. It is the most common condition seen by the gynecologists. PCOS is related to hyper-androgenism, ovulatory dysfunction, and PCO morphology. Other common associations of PCOS are obesity, menstrual irregularity, insulin resistance, and infertility. The patients are at an increased risk of abnormal lipo-proteins, hypertension, and cardio- and cerebrovascular morbidities.

The specific causative agents of PCOS are not clear and heterogeneous nature of syndrome is observed. It seems that it is developed due to accumulation of different diseases sharing several pathophysiological characteristics. Treatment of a patient with PCOS includes lifestyle modifications and pharmaceutical interventions, like oral contraceptives, antiandrogen therapy and insulin lowering medicines. Metformin is usually prescribed in females with PCOS. The resolution of PCOS with metformin can be stimulated further with the addition of medicine, like simvastatin, which also decreases the LH/FSH ratio. Therapy with metformin and simvastatin is in use for the aforementioned conditions.

Metformin is a biguanide which decreases insulin resistance and increase chances of ovulation and pregnancy, followed by declined insulin and androgen levels. Simvastatin is a 3-hydroxy-3-methyl glutaryl co-enzyme A reductase inhibitor. It restricts the cholesterol bio-synthesis. Simvastatin has antioxidant, anti-inflammatory and anti-androgenic properties. It inhibits the proliferation and steroidogenesis of the ovarian theca interstitial cells. Some clinical trials so far have evaluated the effects of combination of simvastatin and metformin with monotherapy of metformin only.

Keeping in view the paucity of ample evidence on these two agents and their role in the management of women with PCOS, the objective of this study was to determine the efficacy of metformin alone and metformin plus simvastatin in the management of women with polycystic ovarian syndrome.

METHODOLOGY
It was randomized controlled trial conducted at the Maternal and Child Health Centre, Unit II, Pakistan Institute of Medical Sciences (PIMS), Islamabad, from November 2014 to April 2015. Ethical approval was taken from Hospital Ethics Committee, Pakistan Institute of Medical Sciences.
Sample size was calculated with WHO sample size calculator with confidence level=95%, margin of error=5%, expected decrease in total cholesterol levels with metformin and placebo=4.2%, and expected decrease in total cholesterol levels with simvastatin and metformin=29.5%. Total study sample was 108 patients, randomly divided into metformin group (n=54) and metformin plus simvastatin group (n=54). Sampling technique was non-probability, consecutive sampling.

The subjects included were women of reproductive age group (15-45 years) with PCOS (endocrinopathy associated with any of the following: hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology). Women having other endocrine disorders, kidney or liver disease, taking oral contraceptive pills or other hormonal medication were excluded.

Informed consent was taken from the patients fulfilling the inclusion criteria. The study patients were selected from both the in-patient and the out-patient departments of the study centre. Detailed clinical history, including menstrual details, was taken with thorough clinical examination performed. Baseline ultrasound was performed to evaluate ovarian size which were considered enlarged with volume more than 10 cc or with more than 12 follicular cysts (size of 2-9 mm) in any one ovary. At baseline intravenous blood samples were taken, by using a 5cc BD syringe and stored in sterile vials to determine the LH/FSH ratio and lipid profile. These were done at Bio Care Laboratory Islamabad. LH and FSH levels were determined on Cobas 411 by electro chemiluminescence and lipid profile was done on Hitachi 902. The report was verified by hematologist. The patients were randomly assigned to oral metformin (500 mg thrice daily) and oral metformin (500 mg thrice daily) plus simvastatin (20 mg once daily). Then patients were followed up in OPD for 3 months with continuation of trial drug. Cases who discontinued the respective medicine were excluded from the study, and replaced with a new case. After three months, blood sample was again obtained to determine the LH/FSH ratio and lipid profile. Reports were assessed and efficacy was labelled, if there was >15% decrease in levels of lipid profile and LH/FSH ratio.

Data was entered in computer using SPSS version 11 (a statistical software) for statistical analysis. Mean ±SD for age, parity, baseline cholesterol, LH/FSH, BMI was calculated. Frequencies and percentages were calculated for efficacy. Chi-square test was applied to compare efficacy between two groups. P ≤0.05 considered as significant.

**RESULTS**

The mean age of the patients was 28.82 ±7.18 years. In this study, the mean BMI was 22.41 ±1.55 Kg/m². The mean LH/FSH ratio at baseline of the patients was 3.458 ±1.38. The mean LH/FSH ratio at the third month of the follow-up was 2.34 ±1.16. The mean total cholesterol value at baseline was 242.84 ±35.40 mg/dL. The mean total cholesterol value at the third month was 168.36 ±16.22 mg/dL.

Efficacy was achieved in 86 patients, out of whom 36 belonged to group A and 50 were from group B. Statistically a significant difference was found between the study groups and efficacy of the patients, i.e. p=0.001.

Efficacy in patients having LH/FSH ratio below 3 at baseline was achieved in 41 cases; in which, 16 were from group A and 25 were from group B (Table I). Similarly, the efficacy in patients having LH/FSH ratio above 3 at baseline was achieved in 45 cases, in which 20 were from group A and 25 were from group B. Statistically, a significant difference was found between the study groups and efficacy of patients having LH/FSH ratio below 3, i.e. p=0.0082.

Table II shows that efficacy was achieved in 36 patients having less than 220 mg/dL total cholesterol value, among whom 29 were from group A and 7 were from group B. Efficacy was achieved in 50 patients having above 220 mg/dL total cholesterol value, out of whom 7 were from group A and 43 were from group B. Statistically, there was significant difference found between the study groups and efficacy of patients among total cholesterol value above 220 mg/dL, i.e. p=0.0004.

Overall efficacy was achieved in 79.6% cases, out of which 66.7% belonged to metformin alone groups and 92.6% were given combination treatment (p=0.001).

<table>
<thead>
<tr>
<th>Study groups</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>Metformin</td>
<td>Metformin+ Simvastatin</td>
</tr>
<tr>
<td>LH/FSH ≤3</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (51.6%)</td>
</tr>
<tr>
<td>No</td>
<td>15 (49.4%)</td>
</tr>
<tr>
<td>LH/FSH &gt;3</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (87.0%)</td>
</tr>
<tr>
<td>No</td>
<td>3 (13.0%)</td>
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</tbody>
</table>

**Table I:** Comparison of efficacy in both study groups stratified by LH/FSH ratio at baseline.

<table>
<thead>
<tr>
<th>Study groups</th>
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<tbody>
<tr>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>Metformin</td>
<td>Metformin+ Simvastatin</td>
</tr>
<tr>
<td>Total cholesterol ≤220 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29 (74.4%)</td>
</tr>
<tr>
<td>No</td>
<td>10 (25.6%)</td>
</tr>
<tr>
<td>Total cholesterol &gt;220 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (46.7%)</td>
</tr>
<tr>
<td>No</td>
<td>8 (53.3%)</td>
</tr>
</tbody>
</table>

**Table II:** Comparison of efficacy in both study groups stratified by total cholesterol at baseline.
Data was also stratified for age. In age <30 years, efficacy was achieved in 21 (61.8%) with metformin, while in 26 (92.9%) with combination (p<0.05). In age ≥30 years, efficacy was achieved in 15 (75%) with metformin, while in 24 (92.3%) with combination (p≥0.05).

DISCUSSION

PCOS is a complex disorder. It is described as raised androgen levels, irregular menstrual cycle, or cysts of small size in one or both side ovaries. It affects at least 7% of females of reproductive age group. According to National Institute of Health, the syndrome develops in about five million females capable of reproduction. About 5-10% females aged 18-44 years develop PCOS. Thus it becomes the most common endocrine anomaly in females of reproductive age group.

In this study, desired efficacy was achieved in 86 (79.63%) cases. Among them, 66.7% with metformin alone while 92.6% with combination of metformin and simvastatin. There was significant difference between both groups. Not much data was published on this topic in literature. In this study, greater efficacy was achieved in combination of metformin plus simvastatin group as compared to metformin alone. Some of the data is discussed here below.

Banaszewska et al. included 113 subjects in their study. With simvastatin alone, DHEAS reduced significantly. But LH or FSH did not decrease either with simvastatin or metformin alone or in combination. Total cholesterol and low-density lipoprotein also reduced significantly with simvastatin and combination of simvastatin and metformin. The number of menses increased and ovarian volume decreased more in patients taking simvastatin. They concluded that simvastatin has better outcome than metformin, but the combination of simvastatin and metformin and simvastatin alone almost had equal results.

Experimental trials showed that metformin can help in reduction of androgen levels significantly, increase insulin sensitivity and stimulate weight loss in females having PCOS. One trial proposed that metformin, if used during pregnancy, has nine times reduction in risk of gestational diabetes in pregnant females with PCOS. As well as, along with prevention from gestational diabetes in pregnant females having PCOS, metformin can also decrease the chance of preeclampsia in these females. Gestational diabetes and preeclampsia usually develop due to deranged levels of lipid profile. So, simvastatin can help in controlling lipid levels and presenting derangement of these levels and thus improves the chances of conception and reduces the risk of gestational diabetes mellitus and preeclampsia.

A longitudinal study proposed that metformin can also help boost up the metabolic system of females with PCOS, if given as 36 months treatment; especially it improves high-density lipoprotein in blood, diastolic blood pressure and BMI. But insufficient data is available, which could recommend the prescription of metformin to all females having PCOS.

On the contrary, the study conducted by Carrick demonstrated that the simvastatin therapy for patients with PCOS appears to possibly result in significant decreases in testosterone levels, and therefore reduce the clinical signs of PCOS. However, simvastatin plus metformin therapy does not provide much, if any, additional reduction in metabolic parameters.

A study by Kazerooni et al. revealed that combination of simvastatin and metformin decreased total cholesterol more than 15% from baseline by 29.5% versus 4.2% with metformin and placebo after 3 months of therapy. LH/FSH ratio significantly decreased by 38.3% and increased by 4.4% after 3 months of therapy with metformin plus simvastatin and metformin plus placebo, respectively. Other meta-analysis and systematic reviews proposed that in females with PCOS having a particular category, metformin can help improve reproductive function regardless of insulin resistance and glucose intolerance. Metformin can also help in reducing significantly liver fat indicators in obese females having PCOS. There is deficiency of evidence regarding the effectivity of simvastatin and metformin combination therapy for PCOS. Larger trials are needed for prolonged period and large sample size to get more evidence regarding beneficial aspects of combination of simvastatin plus metformin and also side effects, if any.

CONCLUSION

The combination of metformin plus simvastatin group showed more efficacious results as compared to metformin alone in treatment of polycystic ovarian syndrome patients. So the combination of metformin plus simvastatin is a better choice for treatment of PCOS in comparison with metformin alone.

Disclosure: The manuscript is based upon the corresponding author's original study for FCPS Part-II dissertation.

REFERENCES


