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Original Research Article

A comparative study of different treatment modalities of polycystic ovarian syndrome in women of reproductive age group at tertiary care centre

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ABSTRACT

Background: Polycystic ovarian syndrome is considered to be a multifaceted disease with a spectrum of manifestation affecting not only women of childbearing age group but also adolescent and post-menopausal women. Most prevalence studies in India prevalence of PCOS as 3.7%-22.5%. Rotterdam consensus conferences, revised diagnostics criteria used. Treatment depends on patient goals ranging from lifestyle modification to drug therapy. It includes: dietary and lifestyle modification, medical management with oral contraceptive pills, metformin, spironolactone, ovulation induction with letrozole, clomiphene.
Methods: Study was conducted in women of reproductive age group with PCOS attending gynaecological OPD at RNT medical college Udaipur. It is a prospective comparative study. Total 290 women included and were followed up for one year.
Results: One year follow up among letrozole group 9 women got conceived, among metformin with letrozole group 23 women got conceived which was statistically significant. Metformin group had significantly greater difference followed by OCP+Metformin group and lifestyle modification group. OCP group and OCP+Metformin group has significant reduction in incidence of hirsutism at one year follow-up. OCP group and OCP+Metformin group had significant reduction in acne at one year follow-up.
Conclusions: Weight reduction is better after metformin along with lifestyle modification than lifestyle modification alone or combine OCP with metformin treatment. Hyperandrogenic symptoms are better responded with OCP then other mode of treatment. Menstrual regularity is well attained by combination treatment of OCP and metformin then monotherapy. Combination of letrozole and metformin is superior as compared to letrozole alone for induction of pregnancy.

Keywords: Letrozole, Lifestyle modification, Metformin, Oral contraceptive pill, Polycystic ovarian syndrome

INTRODUCTION

Polycystic ovarian syndrome is considered to be a multifaceted disease with a spectrum of manifestation affecting not only women of childbearing age group but also adolescent and post-menopausal women.[1] PCOS, by the nature of disease adversely influences the fertility and reproductive health of the affected women.[2] moreover with its association with the other lifestyle disease; it is also the cause of significant cardiovascular and metabolic morbidity.[3] Most prevalence studies in India prevalence of PCOS as 3.7 %-22.5%.[4] According to the 2003, Rotterdam consensus conferences, the revised diagnostics criteria includes any two of the following:[5] Oligomenorrhoea/anovulation, clinical and or biochemical signs of hyperandrogenism, polycystic ovaries on the USG.

For most components of disease, primary treatment is weight loss through lifestyle modification. Treatment options for anovulation: Lifestyle modifications to achieve weight loss (at least 5% of body weight) can increase ovulation and pregnancy rates in some women.[7] Hormonal contraceptives are first line pharmacologic therapy to treat menstrual irregularity for patients who are not trying to become pregnant. Hormonal contraceptives also ameliorate features of hyperandrogenism (hirsutism and acne) and provide endometrial protection through withdrawal bleeding.[8] Consider metformin as second line therapy in patients who cannot take or do not tolerate hormonal contraceptives. Treatment options to address obesity or overweight and to improve metabolic health: First line therapy is lifestyle modification, which includes dietary changes and exercise, to achieve weight loss. Metformin may be added to target metabolic abnormalities (e.g., impaired glucose tolerance, diabetes).[9] Treatment options for acne and hirsutism: Base treatment on patient's degree of distress caused by hirsutism, rather than clinician's quantitative or qualitative assessments. Hormonal contraceptives are first line pharmacologic therapy.[8] If results of hormonal contraceptives are suboptimal, can add antiandrogen drugs (example-spironolactone) after 6 months, preferably in combination with an oral contraceptive (or substituted).[10] Additional useful pharmacologic therapies for symptoms related to hyperandrogenism include: antibiotics, topical retinoids, or isotretinoin for acne, minoxidil for androgenic alopecia, eflornithine for hirsutism, nonpharmacologic cosmetic therapies for hirsutism include shaving, depilating, hair bleaching, electrolysis, and laser hair removal.[12,28] Treatment options for infertility: Lifestyle modifications for weight loss are recommended in patients who are overweight or obese. [11,12] Weight reduction of 5% to 10% in total body weight can increase pregnancy rate and decrease requirements for ovulation-induction agents.[13-14] Both anti-obesity medications and bariatric surgery promote weight loss, but their use is discouraged before infertility treatment owing to safety concerns and mixed pregnancy outcomes.[11] Pharmacotherapy options include clomiphene, aromatase inhibitors, gonadotropins, and metformin. First line pharmacologic therapy for infertility is ovulation induction using either letrozole or clomiphene.[8] Letrozole is superior to clomiphene for achieving pregnancy and live births. Patients with polycystic ovary syndrome are about 50% more likely to have a live birth with letrozole compared with clomiphene.[11,15] Letrozole may be preferred in overweight or obese patients. Clomiphene is an alternative first line agent for ovulation induction owing to more safety data.[15] Second line pharmacologic option for infertility is usually ovarian stimulation using low-dose urinary or recombinant gonadotropins.[16] Cumulative 1- and 2-year singleton live birth rates are approximately 50% and 70%, respectively.[17]Administration and management is complex and ideally is done under guidance of a reproductive endocrinologist. Third line pharmacologic option for infertility is metformin.[18] For the purpose of treating infertility, metformin alone increases ovulation rate but is inferior to other agents such as clomiphene or letrozole.[18] Use of metformin with clomiphene may offer better responses.[19] A combination strategy using metformin with clomiphene may increase pregnancy rates, but the net effect on live births is not known.[20] Can use assisted reproductive technology (e.g., in vitro fertilization) if lifestyle and pharmacologic approaches are unsuccessful.[3] With both reproductive and metabolic treatments, combination therapies (e.g., metformin-clomiphene) generally offer greater benefit.[3]

Drug therapy

I. Hormonal contraceptives: Primarily used to treat menstrual irregularity, but also have modest efficacy in treatment of hirsutism and acne.[21]

a) Selection of oral contraceptive: Daily dose of 20 to 30 mcg of ethinyl estradiol decreases ovarian androgen production. Theoretically, the ideal progestins for an oral contraceptive in polycystic ovary syndrome are third-generation or those with the lowest androgenic profile. Drospirenone and dienogest are considered progestins with minimal androgenicity.[25]

b) For hirsutism, a 6-month trial of oral contraceptive is reasonable, and an antiandrogen drug can be added in combination if there is suboptimal response (usually most effective when used in combination with antiandrogens.

II. Antiandrogens: Primarily used to treat hirsutism (clinical hyperandrogenism), often in combination with an oral contraceptive.[26] Spironolactone (first line antiandrogen for hirsutism and acne): Effective in decreasing degree of hirsutism and, to a lesser extent, acne.[26-28] Spironolactone oral tablet; adult females: 50 to 200 mg/day per oral in 1 or 2 divided doses. Finasteride (second line antiandrogen for hirsutism off-label use).[27]

III. Aromatase inhibitors: Used for ovulation induction Letrozole: Off-label letrozole is a first line therapy used to achieve pregnancy with live birth for sub-fertile women with polycystic ovary syndrome.[29]

IV. Selective estrogen receptor modulators: Used for ovulation induction-clomiphene.

V. Gonadotropin therapy: Typically used for ovulation induction after clomiphene or letrozole. Options include urinary gonadotropins or recombinant follicle-stimulating hormone (live birth rates are similar).[23]

V1. Biguanides: Metformin: Used primarily to improve metabolic status in patients whose condition does not respond adequately to lifestyle measures. Metformin is best used as an adjuvant to lifestyle modification but not as a substitute for it.[14] Has some efficacy in normalizing ovulatory cyclicity but minimal impact on hirsutism.[26] Increases overall pregnancy rates but live birth rates are only marginally increased.[20] Metformin alone is less

effective than clomiphene alone for ovulation induction, clinical pregnancy, and live birth.[24]

VII. Topical eflornithine: Slows growth of unwanted facial hair.[30]

VIII. Minoxidil: Modestly effective for treatment of alopecia.[31]

Nondrug and supportive care include, education: Counsel patient on lifelong nature of syndrome and need for ongoing follow-up to ascertain metabolic status and cardiovascular complications, Lifestyle and weight management counselling.[6] Permanent lifestyle modifications are emphasized in all patients, weight loss improves metabolic parameters, clinical manifestations of androgen excess, and ovulatory dysfunction, reducing insulin resistance through weight loss is important for reducing long-term cardiovascular risks. Advise calorie-restricted diet if patient is overweight or obese. No evidence that one type of diet is superior to another to induce and sustain weight loss.[22] Advise a program with a minimum of 30 minutes of activity daily, or for modest weight loss and greater health benefits, advise a program with a minimum of 250 minutes weekly of moderate intensity activity or 150 minutes weekly of vigorous intensity. [22,14] Aim of this study was to compare the treatment modalities in women with polycystic ovarian syndrome.

METHODS

Study setting

The present study was conducted in women of reproductive age group with polycystic ovarian syndrome attending gynaecological OPD at RNT medical college Udaipur. This was an prospective comparative study conducted from July 2021 to January 2023.

Inclusion criteria

Reproductive age group women (15-45) having clinical symptoms of polycystic ovarian syndrome, participants had to be willing after informed consent in accordance with international and national ethics regulations were included.

Exclusion criteria

Age less than 15 years and more than 45 years, disease presenting with PCOS like feature-hypothyroidism, hyper prolactinoma, ovarian tumor, adrenal tumor and cushing syndrome were excluded from study.

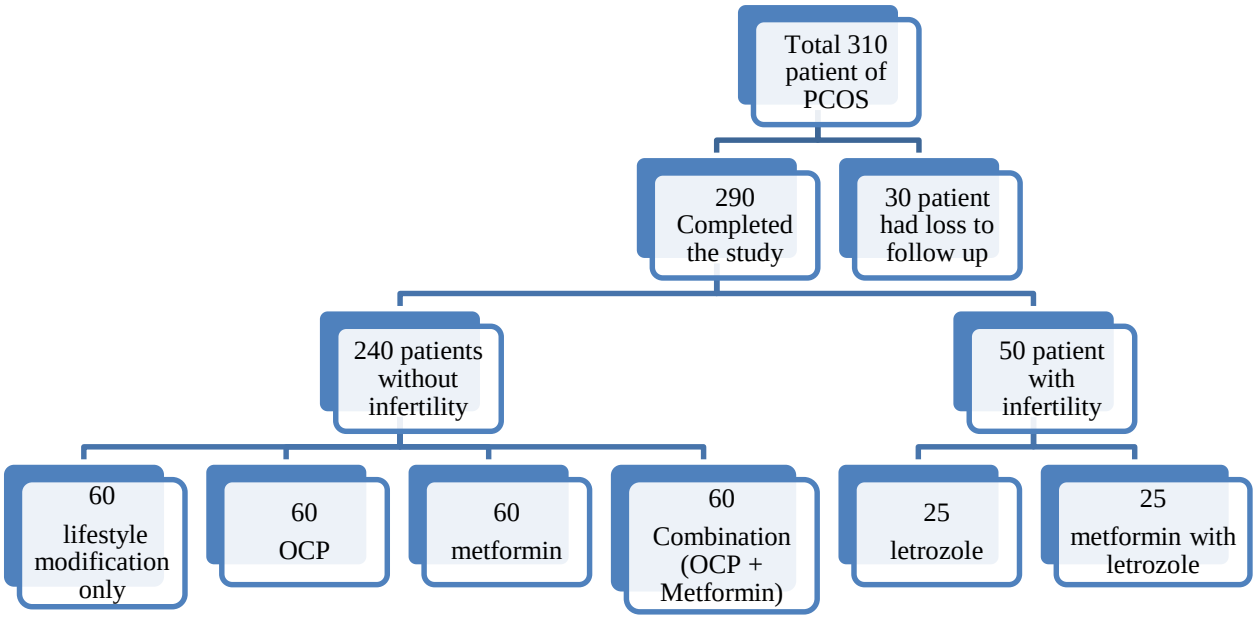

Figure 1: Study participant.

Sample size

According to Shinde et al 2019, the prevalence of PCOS was 21 percent. Based on the prevalence and taking absolute error 5% at 95% confidence interval, the sample size was 255.additional 20% of loss to follow up was added, so the sample size was- n = 255+255×20% =302~ 310.

All the women of reproductive age group attending gynaecology OPD and having clinical symptoms of PCOS were undergone further evaluation for the confirmation of

polycystic ovarian syndrome. After confirmation baseline data was collected with the help of a questionnaire.

We have divided the study population in two parts: patient without infertility (240) and patients with infertility (50).

Among the 240 population the patients were divided in to 4 groups using a computer generated random sequence numbering based on the intervention received: 1) Lifestyle modification only; 2) Oral contraceptive pill (OCP); 3) Metformin; and 4) OCP with metformin combination therapy.

All the groups were comparable in baseline parameters. All the patients were explained about healthy lifestyle measures and weight reduction. 50 patients had infertility so randomly we gave letrozole to 25 patients and combination of metformin with letrozole to 25 patients.

After allocation of the treatment modalities patient were asked to continue their respective treatment and follow up was done at 3 month, 6 month and one year of therapy and change in clinical and metabolic factor was recorded with the help of follow up questionnaire. Patient were counselled for the compliance and proper education was given regarding PCOS to improve the knowledge and awareness for the polycystic awareness syndrome. At the end of study data were analysed.

Statistical analysis

Data are presented as mean, standard deviation, and descriptive statistics were used for the data analysis. ANOVA test and Chi-square test were used to compare the data between the groups. A two-tailed P<0.05 was considered statistically significant for all the tests, and the statistical analysis was done using IBM SPSS Statistics for Windows, Version 26.0., IBM Corp., Chicago, IL.

RESULTS

About 30.7% are having hirsutism, 66.9% overweight, 21.7% acne, 17.2% infertility, 5.9% amenorrhea, 82.4% oligomenorrhea and 21.4% obesity (Figure 2).

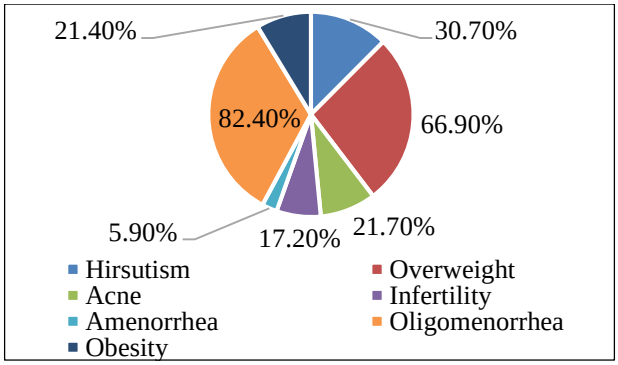

Figure 2: Distribution of chief complaints and other clinic-social factors among the study participants (N=290).

Majority of patients were nulliparous. 93.8% recruited patients had sedentary lifestyle. Majority of patients (93.1%) have irregular menstrual pattern (Table 1).

Table 1: Distribution of treatment among the study participants (N=290).

Treatment	Frequency (240)
Lifestyle modification only	60
OCP	60
Metformin	60
OCP +Metformin	60
Letrozole only	25
Metformin + Letrozole	25

Table 2: Comparison of success of conception in infertile PCOS patients (n=50).

Treatment	Conceived (%)	Didn't conceive (%)	X^2 (df), p
Letrozole only	9 (28.1)	16 (88.9)	17.04 (1), <0.001
Metformin+ Letrozole	23 (71.9)	2 (11.1)	

Table 3: Comparison of effect on BMI across different treatment modalities in women with PCOS (N=290).

Treatment	Body mass index				P	Mean difference
	Baseline	3 months	6 months	1 year		
Lifestyle modification only	24.79±2.06	24.18±1.94	23.40±1.77	22.89±2.11	<0.001	1.89
OCP	26.22±1.47	25.51±1.26	25.09±1.38	26.24±1.63	0.88	-0.18
Metformin	25.35±2.56	24.40±2.67	23.59±2.17	21.92±1.57	<0.001	3.42
OCP + Metformin	25.59±2.49	24.72±2.31	24.95±9.47	22.73±1.87	<0.001	2.86

All the patients were explained about healthy lifestyle measures and weight reduction. At one year follow up among letrozole group 9 women got conceived, among metformin with letrozole group 23 women got conceived which was statistically significant (Table 2).

Table 4: Comparison of effect on acanthosis nigricans across different treatment modalities in women with PCOS (n=63) (n=117).

Treatment	Acanthosis nigricans				P value
	Baseline (n=117) (%)	3 months (n=78) (%)	6 months (n=45) (%)	1 year (n=28) (%)	
Lifestyle modification only	13 (11.1)	9 (11.5)	7 (15.6)	6 (21.4)	0.08
OCP	24 (20.5)	22 (28.2)	20 (44.4)	21 (75)	0.57
Metformin	27 (23.1)	17 (21.8)	9 (20)	0 (0)	<0.001
OC P+ Metformin	25 (21.4)	16 (20.5)	6 (13.3)	1 (3.6)	<0.001

Table 5: Comparison of effect on hirsutism across different treatment modalities in women with PCOS (n=89).

Treatment	Hirsutism				P value
	Baseline (n=89) (%)	3 months (n=40) (%)	6 months (n=25) (%)	1 year (n=22) (%)	
Lifestyle modification only	11 (16.4)	11 (27.5)	11 (44)	10 (45.5)	0.81
OCP	26 (42.6)	6 (15)	2 (8)	1 (4.5)	<0.001
Metformin	12 (19.7)	11 (17.5)	11 (44)	10 (45.5)	0.63
OCP + Metformin	13 (21.3)	12 (30)	1 (4)	1 (4.5)	<0.001

Table 6: Comparison of effect on acne across different treatment modalities in women with PCOS (n=63).

Treatment	Acne				P value
	Baseline (n=63) (%)	3 months (n=43) (%)	6 months (n=28) (%)	1 year (n=28) (%)	
Lifestyle modification only	10 (15.9)	10 (23.3)	10 (35.7)	10 (35.7)	1.00
OCP	20 (31.7)	6 (14)	1 (3.6)	1 (3.6)	<0.001
Metformin	17 (27)	13 (30.2)	14 (50)	14 (50)	0.53
OCP + Metformin	15 (23.8)	14 (32.6)	3 (10.7)	3 (10.7)	0.002

Table 7: Comparison of effect on irregular menstrual pattern across different treatment modalities in women with PCOS (n=270).

Treatment	Irregular menstrual pattern				P value
	Baseline (n=270) (%)	3 months (n=67) (%)	6 months (n=25) (%)	1 year (n=15) (%)	
Lifestyle modification only	57 (21.1)	19 (28.4)	4 (16)	5 (33.3)	<0.001
OCP	55 (20.4)	17 (25.4)	7 (28)	4 (26.7)	<0.001
Metformin	56 (20.7)	10 (14.9)	4 (16)	2 (13.3)	<0.001
OCP + Metformin	60 (22.2)	13 (19.4)	6 (24)	1 (6.7)	<0.001

Although group 1 patients were advised solely lifestyle modification but patients of other groups were also explained about healthy lifestyle measures and weight reduction. Metformin group had significantly greater difference followed by OCP+Metformin group and life style modification group (Table 3).

Metformin group had significantly greater difference followed by OCP+Metformin group and life style modification group (Table 4).

OCP group and OCP+Metformin group has significant reduction in incidence of hirsutism at one year follow up (Table 5).

OCP group and OCP+Metformin group had significant reduction in acne at one year follow up (Table 6).

All the four groups have significant reduction of irregular menstrual pattern (Table 7).

DISCUSSION

BMI: In our study mean body mass index difference between baseline and at 1 year were about greatest in metformin group 3.42 followed by OCP+Metformin group 2.86, lifestyle modification group 1.89, OCP group -0.18. Metformin group had significantly greater difference followed by OCP+Metformin group and life style

modification group. In Sonak et al, 3.49% <18.5, 59.30% 18.51 to 25, 31.40% 25.1-30 and 5.81% 30.1-35.[34] In a study by Kumar et al, mean BMI were of 28.4±6.1 kg/m^2.[32] In a study by Moshin et al, mean BMI of the study participants were 25.49±3.60 among metformin along with letrozole group and 26.01±3.68 among letrozole group.[35]

Menstrual pattern: About 93.1% have irregular menstrual pattern. In Sonak et al, dysmenorrhea (37.21%) was the most common presenting illness followed by amenorrhea (30.23%).[34]

Discussion on Treatment modalities: We have divided the study population in two parts: patient without infertility (240) and patients with infertility (50). Among the 240 population the patients were divided in to 4 groups using a computer generated random sequence numbering based on the intervention received: Group 1 (Lifestyle modification only), Group 2 (OCP), Group 3(Metformin) and Group 4 (OCP with metformin combination). All the patients were explained about healthy lifestyle measures and weight reduction.50 patients had infertility so randomly we gave letrozole to 25 patients and combination of metformin with letrozole to 25 patients.

Comparison of effect on BMI across different treatment modalities in women with PCOS: Our study have showed that treatment with metformin has better weight control and viz a viz better improvement in feature of insulin resistance like acanthosis nigricans. It was followed by combination treatment of metformin with OCP then lifestyle modification. This may be due to deleterious effect of OCP on weight and difficulty of compliance in lifestyle modification. Our results were consistant with Legro et al which had shown that patients using metformin lost weight and those using OCP have gained weight.[22] Essah et al shown that metformin-OCP combination may be of more benefit Than OCP alone in overweight women with PCOS.[39] The study didn't found any significant change in weight with OCP monotherapy. In contrast Kumar et al shows no statistical significant change in weight after 6 month of treatment with OCP alone, metformin alone and combination of both treatment.[33]

Comparison of effect on acanthosis nigricans across different treatment modalities in women with PCOS: Feature of insulin resistance like acanthosis nigricans is better controlled with metformin and combination therapy of OCP and metformin but no significant effect after lifestyle modification only and OCP taking group. These result are consistant with study by Essah et al which reported a threefold improvement in insulin sensitivity with metformin therapy.[39] In a study by Shivangi et al determined the effect of combined oral contraceptives and the combination of cyperoterone acetate and ethinyl estradiol on metabolic syndrome in polycystic ovarian syndrome (PCOS).[38] The patients' waist circumferences and blood pressures were unaffected by either of the medicines, but they did experience an improvement in their fasting blood sugar levels beginning in the third month of treatment. They came to the conclusion that any of the drugs might be utilised to treat people with PCOS, but that diabetic and hyperlipidemic patients should exercise caution when doing so.

Comparison of effect on hyperandrogenism across different treatment modalities in women with PCOS: For control of feature of hyperandogenism like acne and hirsutism both OCP alone and combination treatment of OCP and metformin had significant reduction but there is no significant reduction of hyper andogenism with metformin group and lifestyle only group. This may be because of there is no or very less effect of metformin on hyperandrogenism and poor and less compliance for lifestyle modification. The data were consistent with study by Teede et al demonstrated that OCP therapy for women with PCOS improves hyperandrogenism and menstrual regulation then metformin or other treatment modalities.[40] In a study by Falsetti et al, the effects of a long-term treatment (60 cycles) with the ethinyl oestradiol/cyproterone acetate tablet on polycystic ovarian syndrome were evaluated.[37] Their findings demonstrated that this combination was beneficial in treating androgenic symptoms, particularly acne.In contrast, study by Essah et al demonstrated that metformin-OCP combination reduces the BMI and free testosterone not the OCP treatment.[39]

Comparison of effect on irregular menstrual pattern across different treatment modalities in women with PCOS: Menstrual regularity is well attained by combination treatment of OCP and Metformin then monotherapy. The result were consistent with Kumar et al where menstrual irregularity improved significantly with Metformin-OCP, OCP and metformin alone.[32] But better improvement with combination of metformin-OCP combination than other mode of treatment.

Comparison of success of conception in infertile PCOS patients: In our study at one year follow up among letrozole group 9 women got conceived, among metformin with letrozole group 23 women got conceived which was statistically significant. OCP and life style. Combination of letrozole and metformin is superior as compared to letrozole alone for induction of pregnancy in infertile patients of polycystic ovarian syndrome. These data were consistent with study by Moshin et al, compared the effectiveness of ovulation induction with the combination of letrozole and metformin to the effectiveness of letrozole used alone in patients with infertile polycystic ovarian syndrome.[35] In female patients who have polycystic ovarian syndrome, it is recommended that an induction of pregnancy be attempted with a combination treatment of letrozole and metformin rather than with letrozole alone. In a study by Jiang et al, investigated the effect of letrozole and metformin combined with targeted nursing on ovarian function, luteinizing hormone (LH), and follicle stimulating hormone (FSH) in infertile individuals with PCOS.[36] According to the findings of this research project, the combination of letrozole and metformin has the potential to boost endometrial receptivity and facilitate

patients' physical recoveries. By modulating the hypothalamic-pituitary axis's negative feedback, letrozole tablets can also increase the success rate of inducing ovulation, the rate at which women give birth to full-term babies, and the rate at which they have normal menstrual cycles.

The limitation was compliance regarding the lifestyle modification. We only evaluated the clinical aspect of hyperinsulinemia and hyperandrogenism, not the hormonal profile. Lastly we recommend a larger study to conclude the date in more precise way.

CONCLUSION

It was observed that the most frequent clinical symptoms of PCOS in women were oligomenorrhea, weight gain, infertility, hirsutism, and acne. Weight reduction is better after metformin along with lifestyle modification than lifestyle modification alone or combine OCP with metformin treatment. Hyperandrogenic symptoms are better responded with OCP then other mode of treatment. Menstrual regularity is well attained by combination treatment of OCP and metformin then monotherapy. Combination of letrozole and metformin is superior as compared to letrozole alone for induction of pregnancy in infertile patients of polycystic ovarian syndrome. But the foot note is that lifestyle modification is key for the success of treatment.

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

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