

**EVALUATION OF HORMONAL EFFICACY OF METFORMIN THERAPY IN
POLYCYSTIC OVARY SYNDROME****JaganMohan Chandran^{1,2*}, Mani Vannan^{2,3}, Ashraf Ali²,**¹AIMST University, Semeling, Malaysia.²Sunrise University, Alwar, Rajasthan, India.³Excel College of Pharmacy, Komarapalayam, India.**ABSTRACT**

Objective: To evaluate the metformin response in infertile women with polycystic ovary syndrome, intent to regulate the hormonal profiles with detailed analysis of clinical and laboratory parameters.

Methods: Our study designed a retrospective observational study was conducted between January 2013 and December 2014, A total of 310 patients with PCOS in the age group of 20 to 35 retrieved from medical record, after set a inclusion and exclusion criteria a total of 220 patients with PCOS were included in the study. Evaluation included the collection of laboratory data, efficacy assessment of hormonal parameter like LH, FSH, PL, LH: FSH ratio, and biochemical parameters in PCOS women. Parameters analysed for comparison between pre and post therapy of metformin.

Result: Baseline characteristic like age and weight were measured. Mean age of PCOS women was 26.2 ± 4.78 , and mean weight among PCOS women was 58.76 ± 6.87 . From all patients, 101 subjects had a symptoms of acne and 117 subjects were had symptoms of hirsutism. Metformin therapy significantly reduced incidence of acne and hirsutism. The serum LH, FSH, PL in pre-treatment was 12.69 ± 5.6 , 6.57 ± 1.5 and 18.9 ± 4.9 respectively, and after metformin therapy the LH is 7.68 ± 3.2 , serum FSH 11.32 ± 1.89 and prolactin was 12.32 ± 4.5 , The LH:FSH ratio were > 2 is about 54% women have more than 2 value. Positive response to metformin therapy was associated with significantly different after 2 months of metformin therapy.

Conclusion: This study has shown a remarkable efficacy of metformin in PCOS of patients altered the hormonal levels LH, FSH, PL, and LH; FSH ratio profiles. Thus, it demonstrates that the therapy of metformin was efficient and well tolerated, especially in teratogenicity and resumes the menstrual cyclicality and reduces the acne and hirsutism in PCOS patients.

Keywords: LH, FSH, PL, Metformin, Polycystic Ovary Syndrome

INTRODUCTION

In 1935, Dr.Stein and Leventhal described about poly cystic ovary syndrome (PCOS) amenorrhea, hirsutism on face, obesity and poly cystic ovaries causes hyperandrogenism, menstrual disturbances and anovulation infertility. Hence it's called as Stein Leventhal syndrome, Later these heterogeneous descriptions undergone several revisions and named as PCOS [1-2]. PCOS is now recognized the most recurring endocrine disorder affects approximately 6-15% of the female population in reproductive age [3]. The pathophysiology is unclear, but insulin resistance plays a major role in PCOS [5]. It may affects the post binding signaling and affecting and inhibit the targets, so modulation in steroidogenic pathways [4-7]. The gonadotrophin releasing hormone (GnRH) increased and the consequential

hypersecretion of luteinizing hormone (LH) impacts ovarian androgen synthesis. Elevated LH is thought to play a role in the pathogenesis of PCOS by increasing androgen production and secretion by ovarian theca cells. Insulin resistance, androgen excess and unbalanced hormonal levels, such decrease in follicle stimulating hormone (FSH) and increase in luteinizing hormone (LH), and elevated prolactin (PL), may altered the thyroid-stimulating hormone (TSH) and FSH: LH ratio. These are the classical diagnostic characteristics of PCOS [8-12]. Metformin is a biguanide class of antidiabetic's drugs has been used in infertile women with PCOS who is seeking. The treatment usually depends upon the patient's intent. An anti-hyperglycemic drug metformin improves glucose tolerance, which is lowers the basal and post prandial plasma glucose concentration [13-16]. Metformin increase the glucose uptake in intestinal absorption of glucose and decreases hepatic glucose productions [17-24]. Efficacy of metformin therapy in polycystic ovary syndrome in South Indian population is remains

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unclear, hence our study was undertaken to evaluate the efficacy of metformin therapy in polycystic ovary syndrome.

MATERIALS AND METHODS

Our study group was women presenting between 20-35 years of age with PCOS who visited department of Obstetrics and Gynecology (O&G) in Vaatsalya Hospital, Mandya, Karnataka, India. This study was approved by the Internal Review Boards of Vaatsalya Hospital, Mandya, India, from January 2013 and December 2014. All the subjects' data was retrieved from medical record department of Vaatsalya Hospital, Mandya. The clinical diagnosis of PCOS was based on the Rotterdam criteria suggested that at least two of the following criteria were fulfilled: Chronic oligomenorrhea (10 menstrual cycles in previous year) or amenorrhea and hyper androgenism, (clinical and biochemical), a typical polycystic ovarian morphology by transvaginal ultrasonography, at least one ovary with 10 or more follicle which is 2-8mm in diameter), anovulation and clinical signs of hirsutism. Those who consuming contraceptive pills (oestrogen

progesterone), and drug clomiphene citrate (ovulation induction), male factor infertility, Exclusion criteria of the study group were not taking oral contraceptive medications, and drug clomiphene citrate, male factor infertility, age > 35 years and < 20 years systemic diseases, those who undergone laparoscopy surgery, diagnose with diabetes mellitus and subjects unable to come for regular follow up.

A detailed history was obtained from data and recorded with research pro-forma, the anthropometric data age, body weight, hirsutism and the presence or absence of acne. Before and after metformin treatment therapy the hormonal levels, such as Luteinizing hormone (LH), Follicle stimulating hormone (FSH), Prolactin (PL) and LH: FSA ratio were assess. Totally 310 subjects diagnosed with PCOS in the age group of 20 to 35 years were selected and reviewed and 220 subjects with PCOS were included in our study and remaining was excluded from the study. A biguanide metformin given 850 mg twice a day, after 2 months hormonal evaluated. [Figure 1]

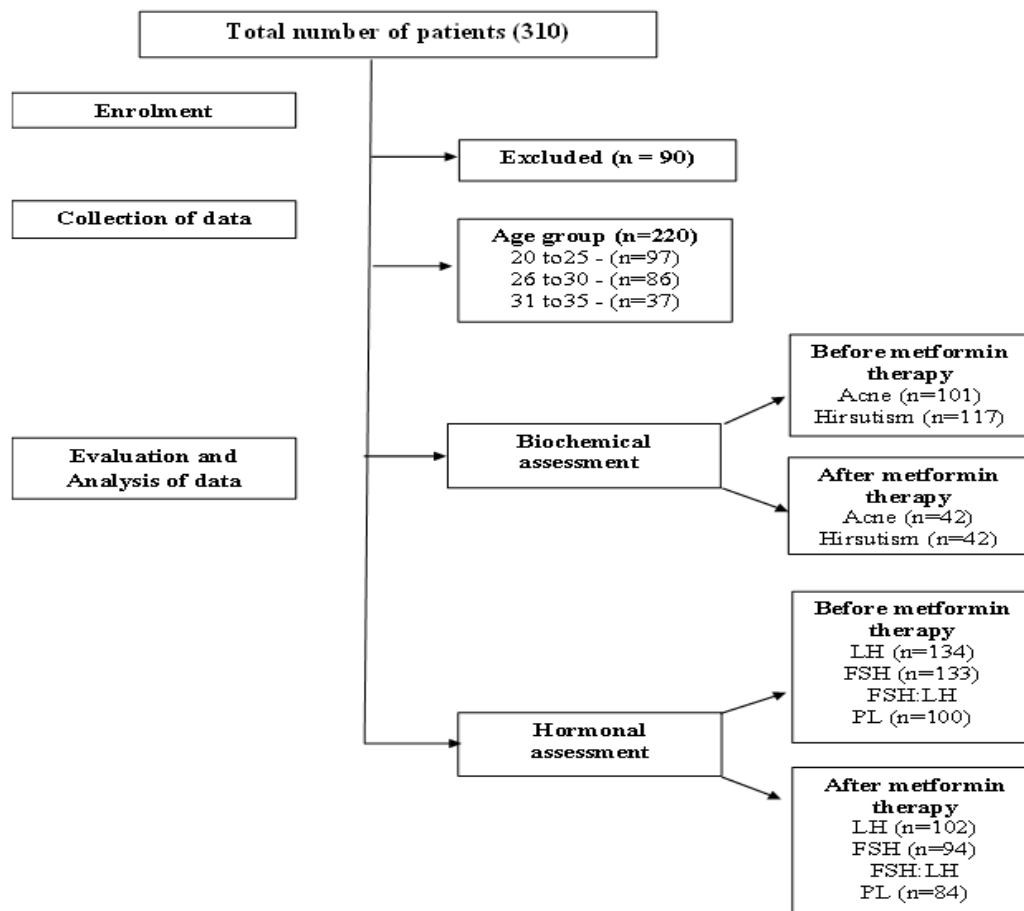


Figure 1: The Flow diagram of study requirement, assessment and follow-up of participants.

Statistical Analysis:

Descriptive statistics were used to summarize the baseline characteristics. The results were summarized as mean ± SD. The hormonal outcomes measured in a group were analysed using pair t-test. Pearson correlation statistic test was used to test variables' responses to the treatment [19]. A *p value* less than 0.05 were considered as significant. All the analysis was performed using SPSS 20.0.

RESULTS

A total of 320 women with symptoms of PCOS were screened for our study, Out of this 90 women were excluded due to not fulfill the criteria, Rest 220 women with PCOS enrolled in our study with mean age of the PCOS women was 26.64 ± 3.64 years in

that 97, 86 and 37 subjects were at the age groups of 20-25, 26-30 and 31-35 years, respectively. The participants' demographic data were listed in Table 1.

Totally 101 subjects had a symptoms of acne and the sign of hirsutism was seen 117 subjects. Metformin therapy significantly reduced the incidence of acne and hirsutism. After metformin therapy the sign of hirsutism reduced to 42. Ferriman-Gallway score or any other standard procedure was not employed to measure hirsutism because of it is out of scope of current study. Metformin therapy outcome present in table 2.

Table 1: Baseline characteristics of the patients

Demographic details	Number (Mean ± SD)
Number of subjects enrolled	310
Number of subjects participated	220
Age (in years)	26.64 ± 3.64
20-25	97
26-30	86
31-35	37
Weight (in kg)	58.76 ± 6.87

Table 2: Summary of metformin therapy outcome

Sing and symptoms	Treatment	Number of Subjects	Age groups		
			18-24	25-30	31-35
Acne	Before	101	86	14	1
	After	42	41	1	0
Hirsutism	Before	117	38	47	32
	After	42	14	13	15

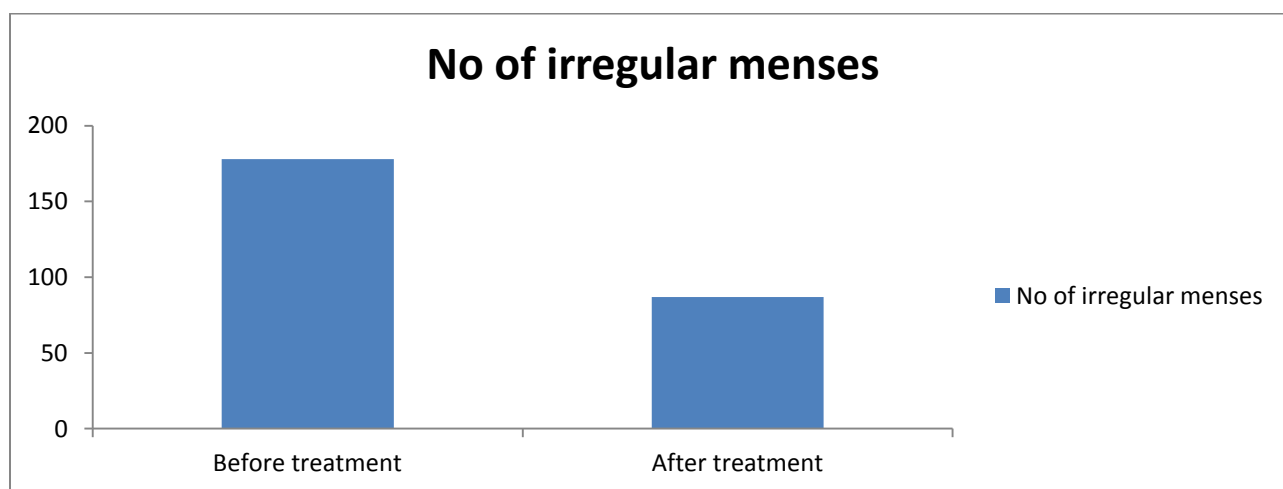


Figure 2: Irregular menses before and after metformin treatment

Prior to metformin therapy, out of 220 subjects 41 subjects has regular menses and remaining subjects were had irregular menses. This was modified by metformin and number of participants with regular menses after metformin therapy were 138 subjects. Patients had irregular menses; the data were presented in the Figure 2.

Table 3 shows the results of hormonal profiles analyzed and the comparison between the baseline and post-treatment values. Mean levels of LH, FSH and PL were significantly different after 2 months of treatment. Mean LH of PCOS women before metformin treatment was 12.69 ± 5.6 mIU/ml and

the after metformin treatment was 7.68 ± 3.2 mIU/ml the $p < 0.02$. Mean FSH of PCOS women before metformin treatment was 6.57 ± 1.5 mIU/ml and the after metformin treatment was 11.32 ± 1.89 mIU/ml the $p < 0.02$. Mean PL of PCOS women before metformin treatment was 18.9 ± 4.9 ng/ml and the after metformin treatment was 12.8 ± 3.2 ng/ml the $p < 0.03$. Reference range for LH for a normal woman is 1.42 -15.4 mIU/ml and FSH as 1.24-7.8 mIU/ml for adult women. PL normal ranges for normal women is 2-17 ng/ml. after metformin reduces the LH : FSH ratio, it was > 2 in 48%; between 1 and 2 in 37% and upto 1 in 15% of PCOS women respectively.

Table 3: Effect of metformin therapy in PCOS

	Before metformin treatment (in number)	After metformin treatment (in number)	<i>p value</i>
LH(mIU/mL)	12.69 ± 5.6	7.68 ± 3.2	0.02
FSH(mIU/mL)	6.57 ± 1.5	11.32 ± 1.89	0.02
PL(ng/mL)	18.9 ± 4.9	12.8 ± 3.2	0.03
LH/FSH	2.45 ± 1.5	1.09 ± 1.1	0.03

DISCUSSION

PCOS is the most common endocrine disorder. It is the mostly cause anovulatory infertility among women of reproductive age, Insulin resistance, hyperandrogenism is a key role in the disorder by increasing androgen concentration and impending ovulation.

The results of our study show that metformin therapy is markedly reduced those who have acne and hirsutism, also improved conception rates. Metformin is an anti-diabetic agents classified under biguanide class. Generally, metformin decreases hepatic glucose production and intestinal absorption of glucose and improve the insulin sensitivity. Our study results shows metformin therapy is reducing the number of acne and hirsutism. Kelly et al [2] also studied the effect of metformin on PCOS and found that metformin had significant improvement in hirsutism at the end of metformin therapy. Metformin also reduced the body weight and normalization of the endocrine milieu to allow regular menstrual cycles, reversal of infertility, and pregnancy. HC Zisser [14] observed that 27% of the study participants were resumed with normal measures and there become pregnant after metformin therapy.

It is probable that insulin resistance and hyperandrogenism alter the secretion of gonadotropins, in favor of an increase in LH [5] and PL, a decrease in FSH, which are PCOS characteristics [8-10]. After metformin therapy in

PCOS women, there was a significant decrease in LH and PL, an increase in FSH, and normalization of the LH/FSH ratio. Metformin therapy has significantly lowered plasma LH (*p-value* 0.02) in the group of women with polycystic ovary syndrome. This result is in agreement with Aqeel Jafar Naji et al [11] who demonstrated a reduction in LH plasma levels in a group of polycystic ovary syndrome PCOS patients undergoing metformin treatment, Though LH hypersecretion in a well-established finding in women with polycystic ovary syndrome but Vincenzo et al [10] warn that demonstration of LH hyper secretion is an insensitive test for symptomatic polycystic ovary syndrome PCOS.

Our results indicate a significant rise in the level of serum FSH levels after metformin therapy. Metformin also appears to improve the ovarian response to FSH in women with polycystic ovary syndrome PCOS. Our study indicates that there was significant rise in the plasma FSH. (*p-value* 0.02). Aqeel Jafar Naji et al [11] observed an increasing in serum FSH levels in a group of polycystic ovary syndrome. Further support of Vincenzo et al [10] also studied the effect of metformin on PCOS and found that metformin had significant improvement in serum FSH level.

Metformin therapy has significantly lowered plasma PL (*p-value* 0.03) in the group of women with polycystic ovary syndrome. This result is in agreement

with J.E Nestler et al [24] who demonstrated a reduction in PL plasma levels in a group of polycystic ovary syndrome patients undergoing metformin treatment.

Our study indicates that there was a significant reduction in LH / FSH ratio (*p-value* 0.03) all the patients who had normalization of menstrual irregularities shown a metformin induced reduction in the insulin level at baseline and after a glucose load that was associated with substantial decreased in LH, FSH ratio. Similar findings have been reported on treatment with insulin sensitizing agent, Nestler [24] suggested a hyperandrogensmism chronically alter the secretion of gonodotropins in favour of an increased in LH, which is typical of polycystic ovary syndrome. Insulin receptors have been identified in human pituitary gland and insulin augment the release of LH by cultured rat pituitary cells.

CONCLUSION

Metformin may be a better therapeutic option for PCOS based on outcomes of hormonal parameters. Our result also suggested to beneficial effects in PCOS patients in regulating the hormonal and clinical parameters, and also reduces hirsutism and acne in certain cases.

CONFLICT OF INTEREST: None

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ABBREVIATIONS USED: PCOS - Poly cystic ovary syndrome, O&G - Obstetrics and Gynecology LH - Luteinizing hormone, FSH - Follicle stimulating hormone, PL - Prolactin, TSH - Thyroid-stimulating hormone, GnRH - Gonadotrophin releasing hormone.

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