

# Study of Efficacy of Combination of Cyproterone Acetate and Ethinyl Estradiol in Androgenic Symptom

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## ABSTRACT

**Introduction:** Androgenic disorders are the most common endocrinopathies of women. The present study was done to study the efficacy and side effects of cyproterone acetate and ethinylestradiol combination for the management of symptoms of hyperandrogenism in females.

**Material and Methods:** The present study was done on 20 females in the Department of Obstetrics and Gynaecology, GRMC, Gwalior. All patients were given combination of cyproterone acetate (2mg) and ethinylestradiol (0.35 µg) from day 1 of menstrual cycle till day 21. Follow up was done 6 months to 1 year for improvement in their presenting complaints of acne, hirsutism and menstrual irregularities.

**Results:** In present study, most (80%) of the female were married, most (65%) of them were having age between 21-30 years. Seventy percent were having acne, 60% had menstrual irregularity and 45% had hirsutism. After 3 cycle, 40% showed disappearance of papules, 71% had improvement in hirsutism in mild cases and 75% patients showed improvement in regular menstrual cycle and normal blood loss during menses whereas, after 6 cycles all patients showed complete disappearance of papules and hirsutism. Only one patient reported severe headache and nausea with the therapy.

**Conclusion:** The combination of cyproterone acetate and ethinylestradiol was effective in reducing the symptoms of hyperandrogenism in females. Effect of drug combination over androgenic symptoms was noted with earliest effect seen over menstrual irregularities which were earliest to normalise within 3 cycles. With the exception of nausea and breast tension in the short term and chloasma with long-term treatment, the therapy was well tolerated.

**Key words:** polycystic ovarian syndrome, hyperandrogenism, acne, hirsutism, menstrual irregularity, cyproterone acetate, ethinyl estradiol

## INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder, which can cause menstrual disturbances, ovulation disorder, miscarriage, pregnancy-related complications and metabolic syndrome.<sup>1</sup> In PCOS, hyperandrogenism is clinically silent in 30% of European women and 80-90% of oriental women or induces hirsutism in 60-83% of women and acne in 11-43% of women.<sup>2</sup> Hyperandrogenism is characterized by excessive production or secretion of androgens which in modest excess leads to clinical symptoms such as increase in sebaceous gland activity leading to acne and increase in sexual hair on locations such as the chin, upper lip, abdomen and chest.<sup>3</sup> The clinical dermatologic manifestations of hyperandrogenism include hirsutism, acne, seborrhea, alopecia, and in severe cases, signs of virilization.<sup>4</sup> Symptomatic therapy based on the main complaint remains the treatment of choice for PCOS. Individualized therapy

should include steroid hormones, antiandrogens, and insulin sensitizing agent.<sup>1</sup>

Accumulation of sebum leads to the formation of comedones which finally results into acne.

Apart from sebum accumulation, colonization of bacteria (*Propionibacterium acnes*) in damaged follicular epithelial cells may also result in to acne. Acne affects around 40-50 million people in the world.<sup>5</sup>

Androgens may also exacerbate the formation of acne by enhancing production of sebum. Most of the PCOS women with acne, may show facial lesions and around 50% of the people have manifested lesions on chest, neck and upper back.<sup>5</sup> Enzyme 5- $\alpha$ -reductase is responsible for regulating androgen bioactivity by converting testosterone to dihydrotestosterone (DHT) which even more potent.<sup>5</sup> Commonly, androgenic symptoms are being treated by oral contraceptives, as they decrease the secretion of adrenal, gonadotrophins or ovarian androgens.<sup>3</sup>

For women with PCOS who do not wish to become pregnant, the combined oral contraceptive (OC) generally is first-line treatment, especially to reduce hirsutism and acne. Although all OCs will suppress ovulation, thereby inhibiting production of androgens in the ovary and reducing serum androgen levels, some OCs are more effective than others in treating clinical signs of hyperandrogenism, depending upon the androgenic properties of the progestin. One strong progestin, cyproterone acetate, acts as an androgen receptor antagonist and effectively reduces hirsutism and acne.<sup>6</sup>

The aim of this study was to investigate the effect of long-term use of combination ethinyl estradiol/cyproterone acetate on the androgenic symptoms in women with PCOS.

## MATERIAL AND METHODS

Study was conducted in the Department of Obstetrics and Gynaecology, Gajra Raja Medical College, Gwalior (M.P.), India. After obtaining consent from female patients suffering with androgenic symptoms like acne, hirsutism or alopecia were included and patients who were pregnant, migraine or with cerebrovascular insufficiency, jaundice or existing liver tumors, undiagnosed vaginal bleeding, history of thromboembolic phenomenon, history of breast or endometrial carcinoma were excluded. Total 20 patients were enrolled

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amongst them 4 were married and 16 were unmarried. Patients were subjected to examination of acne, hirsutism, obesity, general examination, per vaginum examination (if patient is married) and duration of regimen. The acne was graded according to number of comedones, papules, pustules present over face, chest or back as mild <10 score, moderate 10-25 score or Severe >25 score.<sup>7</sup> Hirsutism was graded according to Ferriman Gallway scale in mild 7-9 score, moderate 10-14 score, and severe >=15 score.<sup>2</sup> All 20 patients received combination of cyproterone acetate 2 mg and Ethinyl estradiol 0.35 µg starting from day 1 of their menstrual cycle in cyclic form for 21 days. They were followed upto 6 month to 1 year for improvement in their presenting complaints for acne, hirsutism, menstrual irregularities and whether the patients were satisfied or not with the treatment. Patients were also observed for other side effects.

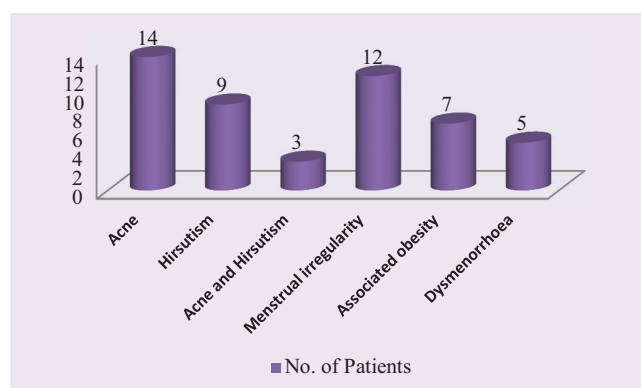
## RESULTS

Out of total 20 female patients with androgenic symptoms, 4 patients were married and 16 patients were unmarried. Age distribution of the patients showed 13 patients were between age 21 to 30 years, 6 patients were below age 20 years and only 1 patient was more than 30 year of age.

Distribution of patients according to symptoms (acne, hirsutism, acne and hirsutism, menstrual irregularity, associated obesity and dysmenorrhoea) is shown in Fig. 1.

Oligomenorrhoea and metropathia haemorrhagica were observed in 12 patients who were having menstrual irregularity. Distribution of patients as per the menstrual irregularity is shown in Table 1.

5 patients were suffering from mild acne, 6 patients were suffering from moderate acne and 3 patients were suffering from severe acne. Effect of the drug combination over acne is shown in Table 2.



**Figure-1:** Distribution of cases according to the presenting symptoms

Sr. No.	Menstrual cycle	Total no. of patients	No. of patients with menstrual irregularity	% Age
1.	Irregular	20	12/20	60%
	Oligomenorrhoea mean cycle duration: 71 days minimum: 40 days maximum: 140 days		10/20	50%
	Metropathiahaemorrhagica		2/20	10%

**Table-1:** Distribution of patients according to menstrual irregularities

Amongst total 20 patients, 14 patients were suffering from acne over face, chest and back. After 3 cycle, about 1/3 of patient recovered and after 6 cycles about 3/4 of patients recovered. Rest of patients was having definite healing of acne and was satisfied with treatment and continued the treatment. 3 patients with severe acne continued treatment for more than 6 cycles and showed complete disappearance of pustules and number of papules to < 10. Their grade improved to mild acne. Facial acne was earliest to improve with back and chest taking longer time for improvement.

Effect of drug combination over hirsutism during the treatment period was observed as per following Table 3.

Overall effect of drug combination on androgenic symptoms is shown in Table 4.

Only one patient was having severe headache and nausea for which she withdrew the treatment. No other patients reported any other side effect.

## DISCUSSION

Persistent acne, hirsutism and menstrual irregularity are typical androgenic disorders caused by excessive androgenic action. Approximately 10-20% of women suffer from disorders related to hyperandrogenism c, the most common endocrinopathy.

The study included 20 patients with androgenic symptoms who were followed for > 6 months.

Most common presenting symptom (70%) was acne over face, chest and back, out of which 5 35% of patients were suffering from mild acne, 43% with moderate acne and 21% were having severe acne. 36% of patients showed improvement in acne after 3 cycles and about 71% of patients recovered after 6 cycles. Rest of the patients had some improvement and were satisfied. Similar result was also found by Gollnick H et al, who reported more than 50% of reduction in papules and pustules after cycle 6. By the end of 6 cycles 64.3% of patients showed a lower grade of acne in their study.<sup>8</sup>

In the present study 9 patients had hirsutism, out which 7 patients (78% of the patients) were having mild and 2 patients (22% of the patients) had moderate hirsutism. In mild hirsutism after 3 cycles, 5 (71.43%) patients reported with change in texture of hair to fine soft and light with no change in frequency of waxing. When treatment was continued for 6 or more cycles, both change in texture and decrease in frequency of waxing were noted. In moderate hirsutism patients, improvement was noted after 6 or more cycles in both change in texture and decrease in frequency of waxing. Overall it was found that at 6 month slight improvement was noted in hirsutism and more improvement was seen only af-

Total no. of patients of Acne			Mild	Moderate	Severe
			5	6	3
Cycle 0 No. of patients	Papule	< 10	5	-	-
		10 to 25	-	6	-
		> 25	-	-	3
	Pustule	< 10	-	6	-
> 10		-	-	3	
Cycle 3 No. of patients	Papule	Disappear	2	-	-
		< 10	3	2	-
		< 25	-	-	1
	Pustule	Disappear	-	-	-
		< 10	-	-	1
Cycle 6 No. of patients	Papule	Disappear	5	2	-
		< 10	-	4	1
		< 25	-	-	2
	Pustule	Disappear	-	6	1
		< 10	-	-	2
> Cycle 6 No. of patients	Papule	Disappear	-	-	-
		< 10	-	-	2
		< 25	-	-	-
	Pustule	Disappear	-	-	3
		< 10	-	-	-

Acne = Mild <10 score, Moderate 10-25 score, Severe >25 score

**Table-2:** Effect of the drug combination over acne

	Cycle 0 No. of patients at the start of treatment	Cycles 3 No. of patients improved		Cycles 6 No. of patients improved		> 6 Cycles No. of patients improved	
		Change in texture of hair (fine, soft, light)	Decrease in frequency of waxing	Change in texture of hair (fine, soft, light)	Decrease in frequency of waxing	Change in texture of hair (fine, soft, light)	Decrease in frequency of waxing
Mild	7 (78%)	5/7	-	7/7	7/7	7/7	7/7
Moderate	2 (22%)	-	-	2/2	-	2/2	2/2
Severe	0 (0%)	-	-	-	-	-	-

**Table-3:** Effect of drug combination over hirsutism during the duration of treatment

Androgenic Symptoms	Cycle 0 No. of patients	Cycles 3		Cycles 6		> 6 Cycles	
		No.	%	No.	%	No.	%
Acne	14	5/14	35%	11/14	78%	14/14	100%
Hirsutism	9			5/9	56%	7/9	78%
Menstrual irregularities	12	9/12	75%	12/12	100%	12/12	100%
Obesity	7	No effect of drug combination seen over obesity					
Dysmenorrhoea	5	-	-	3/5	60%	5/5	100%

**Table-4:** Effect of drug combination over androgenic symptoms

ter longer duration of treatment >6 cycles. Similar results were reported by Morin-Papunen et al, where 20 patients with hirsutism were studied and the hirsutism score was decreased slightly at 6 months.<sup>9</sup>

Effect of drug combination over androgenic symptoms was noted with earliest effect seen over menstrual irregularities which were earliest to normalize within 3 cycles. 75% of patients improved with regular cycle and normal blood loss

during menses. After completion of 6 cycles all patients with menstrual irregularities improved with regular cycles and normal blood loss, 78% of patients of acne showed improvement and 77.78% patients of hirsutism showed improvement with only change in texture of hair. Aydinlik et al, studied 1161 patients of PCOS with dysmenorrhea and reported that this combination has beneficial effects. Complete abolition of dysmenorrhea was seen at 4-12 cycles of treatment which

is comparable to our study.<sup>10</sup>

In our study only one patient had severe headache and nausea after 2 cycles of treatment, which was similar to the previous studies.<sup>10</sup> With the exception of nausea and breast tension in the short term and chloasma with long-term treatment, none of the adverse events usually ascribed to this combination.

## CONCLUSION

It is concluded that combination of cyproterone acetate and ethinyl estradiol is an effective treatment for acne of all grades, all types of lesion and hirsutism with improvement in menstrual irregularities in patients with symptoms of hyperandrogenism. However the limitation of our study is the small study population and further larger studies are needed.

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