VOLUME - 10, ISSUE - 09, SEPTEMBER - 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Gynaecology

"THE EFFECT OF CYPROTERONE ACETATE AND ETHINYLESTRADIOL COMBINATION ON HYPERANDROGENIC AND OTHER SYMPTOMS IN PCOS"

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ABSTRACT

INTRODUCTION- Polycystic ovarian syndrome (PCOS) is a common, heterogeneous disorder affecting 5-15% of women of reproducing age group and characterized by hyperandrogenic skin symptoms, (acne, Hirsutism and female pattern alopecia,) irregular menstrual bleeding, obesity, dysmenorrhea infertility, and increased risk of metabolic syndrome and endometrial cancer.

MATERIAL AND METHOD-The present study was conducted in a private gynecological Clinic Shivpuri, (M.P.). After taking Consent women suffering from PCOS (Fulfilled the clinical and USG criteria of PCOS(Rotterdam criteria)) along with androgenic symptoms like acne, hirsutism and androgenetic alopecia with or without other symptoms like menstrual irregularities and dysmenorrhea were included in the study..

All patients then received a combination of ethenyl Estradiol (0.035mg) + Cyproterone acetate (2mg). The Patients were followed in the third month, Sixth month, and at about 1 year for improvement in various complaints

RESULT- According to presenting symptoms the most common presenting symptom was acne 72.72%, followed by menstrual irregularities 68.18%, hirsutism 50%, alopecia 27.27%, and dysmenorrhea in 27.27%.

In acne patients, 37.5% of patients showed improvement after 3 cycles of CPA/EE, 75% showed at 6 months and in 93.75%, improvement was seen at 12 months. In the case of alopecia (83.33%) patient showed improvement after >6 cycles. Patients with hirsutism showed no improvement after 3 months of therapy but 54.54% of the patients showed a change in texture after 6 months of therapy and 72.72% after 9-12 months of therapy. Patients with dysmenorrhea reported a decrease in pain after therapy.

The acceptance of the treatment was very good. In 86.36% of patients, good tolerance of drug was seen and in only 3 patients adverse effects (headache and nausea) of the drug were there.

All the patients were having good to moderate satisfaction with the therapy.

CONCLUSION- Since androgen excess is the prime defect in polycystic ovarian disease, its reduction is the main therapeutic target for most women. Our study found that combined hormonal contraceptives containing ethenyl Estradiol (0.035mg) + Cyproterone acetate (2mg) in a 21/7 regimen had a positive effect in the treatment of acne, hirsutism, menstrual irregularity, and dysmenorrhea in PCOS patients.

KEYWORDS : Hirsutism, alopecia, acne.

1. INTRODUCTION-

Polycystic ovarian syndrome (PCOS) is a common, heterogeneous disorder affecting 5-15% of women of reproducing age group and characterized by hyperandrogenic skin symptoms, (acne, seborrhea, Hirsutism, female pattern alopecia,) irregular menstrual bleeding, obesity, dysmenorrhea infertility, and increased risk of metabolic syndrome and endometrial cancer. Excessive biosynthesis and secretion of androgen by ovarian theca cells and in many cases, by adrenal reticularis cells, is the main pathogenetic mechanism of PCOS.[1,2] In addition, hyperinsulinism and insulin resistance enhance ovarian and adrenal androgen secretion in these women.[3]

Hirsutism is the most sensitive marker for increased levels of androgen (Hyperandrogenism) and is present in 70% of women with PCOS.[4] Acne is a less prevalent and less specific marker of elevated androgens (Hyperandrogenism) and is present as a symptom in approximately 15% of women with PCOS. [5] Both hirsutism and acne can significantly and negatively impact the quality of life and cause anxiety and depression. [6,7] Female androgenic alopecia affects approximately 35% of women with PCOS and can occur either in isolation (rarely) or in association with other skin symptoms of Hyperandrogenism. [8] Acne can be found in 36 to 50% of patients with PCOS, other symptoms like Menstrual disorders are also one of the commonest symptoms and are seen in 60-85 % of PCOS patients. Obesity is seen in about 50% of patients. Infertility is very common and may be presenting feature in 40-50% of Women. Dysmenorrhea is less commonly seen in PCOS patients.[9]

Enzyme 5-α-reductase directly influences the degree of androgenic effect on hair growth. With the increased level of circulating androgen or increase activity of 5-α-reductase, terminal hair appears where normally only vellus hair is present. With this alteration, the length of the anagen phase is prolonged and the hair becomes thicker. the excessive 5-α-reductase activity also may lead to acne as well as scalp hair loss (alopecia). [10]

Hirsutism is defined as excessive androgen-dependent (male pattern) terminal hair growth occurring in women. Terminal hair mini-present on the upper lip, on the chin, around the nipples, and along the linea alba of the lower abdomen.

Androgens may also exacerbate the formation of acne by enhancing the production of sebum. Apart from sebum accumulation, colonization of bacteria (Propionibacterium acnes) in damaged follicular epithelial cells may also result in acne. Facial lesions may also be present in most of the women who have PCOS with acne. Approximately 50% of the people have manifested lesions on the chest, neck, and upper back.[11] Acne, Vulgaris is a multifactorial disease and is androgen-dependent and affects skin with an increased number of oil glands. It is characterized by an area of comedones blackheads (Open plugged pores) and whiteheads (closed plugged pores)], papules (small red tender bumps),

pustules(papules with pus and their tips), nodules (large solid papules), cystic lesions (painful pus-filled lumps under the skin) and scarring.[12] Androgen influences sebaceous glands and sebum production.

Cyproterone acetate (CPA) 2mg, combined with ethinylestradiol (EE) 35g, is indicated for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhea), androgenic alopecia and/or hirsutism, in women of reproductive age group.

The primary mechanism of action of CPA/EE (COCs) is the suppression of ovulation- (Committee)[13]. The estrogenic component in COCs causes an increase in the production of sex hormone-binding globulin (SHBG), which leads to a decrease in circulating free testosterone. In addition mainly through the action of progestogens, COCs directly suppress the production of androgens in the ovaries and to a lesser degree, in the adrenal glands.[14, 15] Antiandrogenic progestogens, Cyproterone inhibit the enzyme 5α-reductase, which converts testosterone to dihydrotestosterone, the latter being the form that binds to cellular receptors.[15,16]. The changes in androgen levels vary depending on the individual concerned.[15]. Although the levels of testosterone and free testosterone are reduced in CPA/EE users, Improvement of biochemical hyperandrogenism with CPA/EE increases fertility and improved pregnancy outcome. It also works as a contraceptive, reduces irregular bleeding and dysmenorrheal. Long-term benefits are reduction in metabolic syndromes, the onset of new diabetes, and endometrial malignancy.

Cyproterone acetate/Ethinyl estradiol is generally well tolerated with a side effect profile similar to that seen with COCs. Side effects include nausea, headaches, breast tenderness, weight gain, and loss of libido.

Combined hormonal treatments, including COCs and antiandrogenic progestogen/EE combinations, are associated with an elevated risk of venous thromboembolism (VTE) when compared to the risk in non-users. The PRAC review suggested that the known risk of thromboembolism which is rare with CPA/EE should be discussed with the patients. The increased risk is associated with age, obesity, smoking, and prolonged immobility.[17] European

OBJECTIVE- The objective of this study was to evaluate the effect of CPA/EE in patients with mild to moderate acne, alopecia, hirsutism, and other clinical symptoms and to note the drug reactions and adverse effects in patients taking CPA/EE.

INCLUSION CRITERIA-

18-40 years non-Pregnant females with mild to moderate acne, hirsutism, and androgenic alopecia grade I-II and other symptoms of PCOS were included in this study.

EXCLUSION CRITERIA-

Women more than 40 years, patients who were pregnant & breastfeedings mothers, patients who were obese, had a H/O smoking, cerebrovascular insufficiency, Jaundice, H/O of thromboembolic disease, H/O breast or endometrial carcinoma were excluded.

2. MATERIAL & METHODS-

The present study was conducted in a private gynecological Clinic Shivpuri, (M.P.). After taking Consent women suffering from PCOS (Fulfilled the clinical and USG criteria of PCOS(Rotterdam criteria)) along with androgenic symptoms like acne, hirsutism, androgenetic alopecia with or without other symptoms like menstrual irregularities and dysmenorrhea were included in the study.

A total of 22 Patients was included in the study. After detailed history taking, general examination for acne, BMI, waist-hip ratio, Ferryman Galway scoring for hirsutism, and other features of PCOS were noted. Per Abdomen and pervaginal examination (in married women) was carried out. All patients then received a combination of ethenyl Estradiol (0.035mg) + Cyproterone acetate (2mg) which started from the first day of the menstrual cycle for 21 days followed by a 7 days rest period. A total of 12 treatment cycles were completed during the study period. The Patients were followed in the third month, Sixth month, and at about 1 year for improvement in various complaints about acne, hirsutism menstrual irregularity, and dysmenorrhea. Patient satisfaction and any adverse effects due to the treatment were also studied.

3. RESULTS-

Table 1– Demographic and clinical characteristics of the study group.

Age of patients	Number	%
<20 years	8	36.36
21-30 years	12	54.54
>30 years	2	9.09
Total	**22**	100
Marital status		
Married	8	36.36
Unmarried	14	63.63
Total	**22**	100
F-G score for Hirsutism		
Normal <8	0	0
Mild (9-16)	6	54.54
Moderate (17-25)	5	45.45
Severe (>25)	0	0
Total	**11**	
Acne		
Grade I:- Simple non-inflammatory acne comedones and a few papules.	5	31.25
Grade II :- Comedones, papules and a few pustules.	11	68.75
Grade III:-Large inflammatory papules, pustules and a few cysts a a more severe form involving the face, neck and upper portions of the trunk.	0	0
Grade IV:-More severe, with cysts, becoming confluent.	0	0
Total	**16**	100
Alopecia		
Grade I -Thinning of the hair on the crown. 1-3 cm behind the frontal hairline.	5	83.33
Grade II - Pronounced rarefaction of the hair on the crown within the area seen in Grade I.	1	16.66
Grade III - Full baldness within the area seen in grade I & II.	0	0
Total	6	100

Most (54.54%) of the patients were between the age of 21-30 years, most of them were unmarried (63.63%). Out of 11 patients showing hirsutism, 6 were of mild (54.54%) FG score (9-16) and 5 were of moderate FG score (17– 25). In 16 patients, acne was of grade 1 (31.25%) and grade 2(68.75%).In 6 patients with alopecia cases, most of them were grade 1(83.33%)

Table 2 – Distribution of cases according to presenting symptoms.

Androgenic & other Symptoms	No. of patients	Percentage
Acne	16	72.72
Alopecia	6	27.27
Hirsutism	11	50
Menstrual irregularities	15	68.18
Dysmenorrhea	6	27.27

According to presenting symptoms the most common presenting symptom was acne 72.72%, followed by menstrual irregularities 68.18%, hirsutism 50%, alopecia 27.27%, and dysmenorrhea in 27.27%.

Table 3 – Affect of CPA/EE over androgenic symptoms and other clinical characteristics

Androgenic Symptoms	Cycle 0 No. of patients	Cycles 3		Cycles 6		>6 Cycles	
		No.	%	No	%	No	%
Acne	16 (72.72)	6	37.5	12	75	15	93.75
Alopecia	6 (27.27)	1	16.66	3	50	4	83.33
Hirsutism	11(50)		-	6	54.54	8	72.72
Menstrual irregularities	15 (68.18)	11	73.33	14	93.33	15	100
Dysmenorrhea	6 (27.27)	1	16.66	4	66.66	6	100

In acne patients, 37.5% of patients showed improvement after 3 cycles of CPA/EE, 75% showed at 6 months and in 93.75%, improvement was seen at 12 months. In the case of alopecia (83.33%) patient showed improvement after >6 cycles. Patients with hirsutism showed no improvement after 3 months of therapy but 54.54% of the patients showed a change in texture after 6 months of therapy and 72.72% after 9-12 months of therapy. Patients with dysmenorrhea reported a decrease in pain after therapy.

Table 4 - Acceptance of the treatment.

Acceptance of the treatment	Numbers	Percentage
No adverse reaction (good tolerance)	19	86.36
Adverse effects (Nausea Headache, Asthma)	3	13.63

In 86.36% of patients, good tolerance of drug was seen and in only 3 patients adverse effects (headache and nausea) of the drug were there. All the patients were having good to moderate satisfaction with the therapy.

4. 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, the most common endocrinopathy.

This study was conducted to assess the effect of the combination of ethenyl Estradiol (0.035mg) + Cyproterone acetate (2mg) on women suffering from PCOS with androgenic symptoms. The Patients were followed in the third month, Sixth month, and at 1 year for improvement in various complaints about acne, hirsutism menstrual irregularity, and dysmenorrhea.

In our study, a total of 22 patients participated, out of which 8 patients (36.36%) were below 20 years of age. 12 patients (54.54%) belonged to the age group between 21 to 30 years and 2 patients (9.09%) were above 30 years of age. 8 women (36.36%) enrolled in the study were married and 14 (63.63%) were unmarried.

In this study, we further measured the **Ferryman Gallwey** score for hirsutism and observed that out of 22 women who participated in the study, 11 had hirsutism. 6 women (54.54%) had a mild score lying between 9 – 16. 5 women (45.45%) had a moderate score lying between 17 to 25. No women had a severe scoring for hirsutism. These percentages are similar to those observed in their study by **Shrivastava R et al.**[18] In their study, out of 20 patients, 9 patients had hirsutism, out of which 7 patients (78% of the patients) were having mild and 2 patients (22% of the patients) had moderate hirsutism.

Regarding another symptom of PCOS i.e acne, our analysis was that 16 women suffered from it. Out of these 16 women, 5 (31.25%) had grade I involvement, 11 (68.75%) women had grade II acne involvement. None of the women had grade III and grade IV involvement. This suggests that a maximum number of women had comedones, papules along with a few pustules.

Alopecia was present in 6 women out of 22. 5 women (83.33%) had grade I alopecia that is thinning of hair on the crown, 1 to 3 cm behind the frontal hairline. Rest 1 woman (16.66%) had grade I alopecia. None of the women presented with grade III alopecia. Our study shows a correlation between androgenic alopecia and PCOS. A study conducted by **Cela E et al**[19] concluded that PCOS was common in a large multiethnic group of women with androgenic alopecia (67% compared with 27% in the control group), confirming an association between PCO morphology and alopecia.

According to presenting symptoms the most common presenting symptom was acne (72.72%), followed by menstrual irregularities (68.18%), hirsutism (50%), alopecia, and dysmenorrhea (both 27.27%). According to **Shrivastava R et al** [18] also, the most common presenting symptom (70%) was acne over the 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. This finding is very much similar to our study.

In acne patients, 37.5% of patients showed improvement after 3 cycles of CPA/EE, 75% showed at 6 months and 93.75% of improvement was seen at 12 months. These findings are in agreement with the study done by **Gollnick H et al 20,** 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.

In the case of alopecia (83.33%) patient showed improvement after >6 cycles. This finding of our study is in agreement with a study done by **Amiri M et al** [21] which stated that cyproterone acetate can effectively suppress gonadotropins, leading to a decrease in androgenic parameters especially alopecia.

Patients with hirsutism showed no improvement after 3 months of therapy but 54.54% of the patients showed a change in texture after 6 months of therapy and 72.72% after 9-12 months of therapy. Similar results were reported by **Morin-Papunen L et al**[22], where 20 patients with hirsutism were studied and the hirsutism score was decreased slightly at 6 months. Overall it was found that at 6 months slight improvement was noted in hirsutism and more improvement has been seen only after a longer duration of treatment >6 cycles.

Patients with dysmenorrhea reported a decrease in pain after therapy in our study. **Aydinlik et al** [23] 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.

In this study, 19 patients (86.36%) showed good tolerance towards the therapy with no adverse reactions. 3 patients (13.63%) had adverse effects like nausea, vomiting, and headache. Conclusively all the patients showed good to moderate satisfaction with the treatment. **Bitzer J et al**[24.] wrote a review on the use of cyproterone acetate/Ethinyl estradiol in hyperandrogenic skin symptoms. They identified seventy-eight studies and concluded that the majority of sufficiently powered studies showed high efficacy of CPA 2mg/EE 35 μg in the treatment of severe acne and hirsutism. Studies showed that the therapeutic response in women with hirsutism requires a long-term approach and that hyperandrogenic skin symptoms in patients with PCOS are efficiently treated. These findings are in agreement with our studies.

5. CONCLUSION-

Since androgen excess is the prime defect in polycystic ovarian disease, its reduction is the main therapeutic target for most women. Our study found that combined hormonal contraceptives containing ethenyl Estradiol (0.035mg) + Cyproterone acetate (2mg) in a 21/7 regimen had a positive effect in the treatment of acne, hirsutism, menstrual irregularity, and dysmenorrhea in PCOS patients. During Evaluation of patients for treatment with CPA/EE doctors and health care providers should take care of acquired or genetic risk factors such as advanced age, smoking, obesity, hereditary, thrombophilia, history of cardiac disease, history of thromboembolic disease, and immobility.

Future development in the field of the anti-androgenic drug may be more effective in the unmet management area of hyperandrogenic PCOS Patients.

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