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To evaluate the outcome of combined therapy of cyproterone acetate and ethinyl estradiol in PCOS

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Abstract

Background: This study was conducted at Index Medical College Hospital & Research Centre, Indore from July 2018 to June 2019.

Method: A detailed clinical, menstrual, past history & family history was obtained at the first visit of the patient. The time of onset of hirsutism, acne, alopecia or menstrual dysfunction was asked in order to determine the duration of clinical hyperandrogenism. The onset of weight gain was also noted.

Result: Out of 84 cases, 61 were married (72.62%) and 23 were unmarried (27.38%),

Conclusion: CPA+EE place an important role in improving the outcome of ovulation induction in Clomiphene citrate resistant cases. Side-effects like head ache, nausea, depression, nervousness have been observed which are significant. When selecting a contraception for subjects, suffering from androgenic symptoms, in the light of encouraging data and unique features, CPA-EE combination could be the logical therapy of choice. The need of the hour is to individualize the treatment modality for each PCOS woman.

Keywords: Therapy, Cyproterone Acetate, Ethinyl, Estradiol & PCOS.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age globally [1]. It affects 6–21% of women when assessed using the Rotterdam criteria [2]. Clinical presentation can vary widely but, in general, PCOS is characterized by irregular menses, hyperandrogenism (with either clinical symptoms or assessed by laboratory data) and polycystic ovary morphology, after excluding other endocrine causes such as hyperprolactinemia [3]. The ongoing confusion and debate around which criteria to use when diagnosing PCOS led to extension of the Rotterdam criteria to phenotypic definitions, which not only help with clinical research and practice but also aid the identification of women with PCOS who are at long-term metabolic risk.

Polycystic ovarian syndrome (PCOS) is an heterogeneous disorder characterized by abnormal gonadotrophin secretion, chronic anovulation, hyperandrogenism and a variety of meta-bolic effects such as obesity (30–60%) and insulin resistance present in 30–46% of lean and in 57–78% of obese women [4]. The alteration of the system insulin/insulin-like growth factor-I (IGF-I)/insulin-like growth factor-binding proteins (IGFBPs), in synergy with LH, promotes the mitotic activity and hyperplasia of the ovary theca/stromal compartment in PCOS and increases androgen production (Duleba *et al.*, 2002) [5].

Material & Method

This study was conducted at Index Medical College Hospital & Research Centre, Indore from July 2018 to June 2019. A detailed clinical, menstrual, past history & family history was obtained at the first visit of the patient. The time of onset of hirsutism, acne, alopecia or menstrual dysfunction was asked in order to determine the duration of clinical hyperandrogenism. The onset of weight gain was also noted.

Informed written consent was taken after explaining the whole procedure. Menstrual history: Age at menarche, past menstrual cycles, present menstrual cycles, amount of blood loss (oligomenorrhoea /menorrhagia/ amenorrhoea/normal).

- Regular menstrual cycles: An average cycle length between 22- 41 days, one or no cycle with a length of <22 & >41 days during the past one year.

- Irregular menstrual cycles: An average cycle length between 22 & 41 days, two or more cycles with a length of <22 & >41 days during the past one year.
- Oligomenorrhoea: An average cycle length between 42 & 180 days.
- Secondary amenorrhoea: Absence of menstruation for 180 days or more.

Marital status: Married/ Unmarried

After initial workup including obstetric history, menstrual pattern, past & present history, the following clinical parameters were measured:

- Height (in metres)
- Weight (in kgs.)
- BMI (Body mass index): Weight (kg.)/height(m²)
- WHR (Waist: hip ratio) - A plastic tape was used for measuring waist circumference (midway between the lowest rib margin & iliac crest in standing position), & hip was measured at the broadest part of the lower body, usually at the level of trochanters.
- Breast development, pubic & axillary hair development was scored according to the stages described by Tanner.
- Body hair grading was assessed according to the Ferriman Galleway score as per proforma
- Abnormal hair growth was defined as Ferriman Galleway score of 1-7.
- Hirsutism as a F.G. score of 8 or more.
- Acne were evaluated in four grades:
 - Grade 0- No acne.
 - Grade 1- Minor acne on face only.
 - Grade 2- Moderate acne on face only.
 - Grade 3- Severe acne on face & back or chest.

Also, the following information was taken regarding H/O any contraceptive use, H/O any treatment taken for infertility, duration of living with husband, H/O any surgery, family history of hypertension, diabetes, T.B.

I. Clinical

Patients with signs and symptoms suggestive of:

- Hyperandrogenism such as hirsutism, acne, alopecia
- Clinical signs of hyperinsulinemia such as obesity and acanthosis nigricans
- Menstrual abnormality – oligomenorrhoea, amenorrhoea, irregular cycles or dysfunctional uterine bleeding
- Infertility – primary or secondary

II. Laboratory Investigations:

Basic investigations like haemogram, with ESR, FBS/PPBS, blood urea, serum creatinine, VDRL – both of husband and wife, urine R/M, chest X-ray – PA view, Mantoux test and husband's semen analysis

- Raised serum LH >8 IU/ml
 - Decreased or normal serum FSH – 10 IU/ml^[55-56]
 - LH : FSH > 2-3 : 1
- GTT – impaired
- Serum fasting insulin - raised > 25 µg/ml
- Serum DHEA – raised
- Serum testosterone – raised (normal 20-80 ng/ml)
- Serum prolactin raised (Normal < 50 ng/ml)

Exclusion Criteria

- Patients with history of diabetes mellitus

- History of drug intake such as glucocorticoids, oral contraceptives, within 3 months of recruitment of cases
- Known cases of bilateral tubal disease
- Androgen secreting tumour
- Presence of endocrinopathies causing amenorrhoea such as thyroid disorders or pituitary insufficiency.

Results

Table 1: Table showing distribution of cases according to Marital status (n=84)

Marital Status	No.	Percentage
Married	61	72.62
Unmarried	23	27.38
Total	84	100

Out of 84 cases, 61 were married (72.62%) and 23 were unmarried (27.38%)

Table 2: Table showing analysis of concurrent side effects with CPA-EE therapy

Side effects	Baseline		12 cycles	
	No.	Percentage	No.	Percentage
Headache	5	5.9	10	11.9
Nausea & vomiting	2	2.3	5	5.9
Breast tenderness	2	2.3	4	4.7
Nervousness	3	3.6	5	5.9
Depression	3	3.6	6	7.1
Edema	1	1.1	1	1.1

In our study, out of 84 patients, the no. of patients complaining of constant headache rose from 5 (5.9%) cases at baseline to 10 (11.9%) cases after 12 cycles of treatment. At the end of 12 cycles of therapy, incidence of nausea and vomiting increased from 2.3 % to 5.9%, of breast tenderness from 2.3% to 4.7% of nervousness from 3.6% to 5.9% of depression from 3.6% to 7.1%. The increase in incidence of edema was not reported in our study.

Favourable effects were also seen in terms of the pregnancy rate after discontinuation of CPA+EE therapy as 12/84(7%) cases conceived within six months after stopping the therapy.

Discussion

Concurrent side effects

Several side effects like headache, migraine, reduced libido, breast tenderness, chloasma, nervousness, depression, edema, nausea and vomiting are observed with CPA-EE therapy. Results of present study are compared with those of R. Erkkola, E. Hirvonen, J. Luikku, *et al* (Finland) (1990)^[16] and were as follows:

Table 3: Side Effects

Side Effects	R. Erkkola ^[6] , E. Hirvonen, J. Luikku <i>et al.</i> study			Present study		
	Baseline	12 cycles	% Diff.	Baseline	12 cycles	% Diff
1. Head ache	6.9	11.3	4.4	5.9	11.9	6%↑
2. Breast tenderness	1.5	2.9	1.4	2.3	4.7	2.4%↑
3. Nervousness	2.2	3.1	0.9	3.6	5.9	2.3%↑
4. Depression	2.6	4.3	1.7	3.6	7.1	3.5%↑
5. Oedema	3.9	4.3	0.4	1.1	1.1	-

The results of the present study were comparable to R. Erkkola

et al study [6]. Also, it was observed that with CPA+EE therapy, headache is the most common and pronounced side effect and on application of statistical tests, it was found to be significant ($p < 0.05$).

There was no increase in the incidence of oedema. Thromboembolic complications or hepatopathies were not observed in the present study [7].

CPA+EE combination therapy had no effect on WHR (Waist:Hip ratio). Slight rise in BMI (Body Mass Index) was observed with this treatment for 12 cycles [8]. But, this was found to be statistically insignificant ($P = 0.09$)

Despite the length of the study, the dropout rate for adverse events was only 3.2% (3 out of 93 women).

Conclusion

CPA+EE place an important role in improving the outcome of ovulation induction in Clomiphene citrate resistant cases. Side-effects like head ache, nausea, depression, nervousness have been observed which are significant. When selecting a contraception for subjects, suffering from androgenic symptoms, in the light of encouraging data and unique features, CPA-EE combination could be the logical therapy of choice. The need of the hour is to individualize the treatment modality for each PCOS woman.

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