

Effect Of The Combination Of Ethinyl Oestradiol And Cyproterone Acetate On Menstrual Regulation, Endocrine And Ultrasonographic Profile In Single Women With Polycystic Ovary Syndrome

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Abstract

The aim of the study was to investigate the effect of administration of cyproterone acetate / ethinyl oestradiol (CPA/EE) combination (Diane 35) on the menstrual regulation, endocrine and ultrasonographic profile in women with polycystic ovary syndrome(PCOS). 17 single PCOS patients were treated with 2 mg cyproterone acetate and 35µg ethinyl oestradiol for 12 cycles. Assessment of menstrual cycle pattern, ultrasonographic pelvic examination and evaluation of the hormonal profile were performed at base line and after three, six and 12 months of treatment. All women attained satisfactory cycle control. Plasma level of luteinizing hormone (LH) , testosterone significantly fell from the third cycle on with a significant decrease in ovarian size and volume and a reduction in microcysts number and size. The CPA/EE combination seems to be effective in ameliorating ultrasonographic, clinical and hormonal features of PCOS.

Introduction

The polycystic ovary syndrome is a heterogeneous collection of signs and symptoms that gathered together form a spectrum of a disorder with mild presentation in some, while in others a severe disturbance of reproductive, endocrine and metabolic function⁽¹⁾. It was described for the first time in 1935⁽²⁾. A wedge resection of the ovaries in a series of seven patients showed in each wedge 20-100 follicular cysts of 1-15 mm, when full thickness ovarian cross-section of polycystic ovaries were histologically examined and compared to controls it was found that polycystic ovaries had double the number of antral follicles, a thickened tunica and an increased stroma⁽³⁾.

The definition of the syndrome has been much debated. Abnormal gonadotropin secretion, chronic anovulation, an elevated circulating androgen levels variably combined represent the pathophysiological background for the appearance of menstrual irregularities, infertility, obesity, hirsutism and acne ⁽⁴⁾.

As the exact basic aetiology of poly cystic ovary syndrome (PCOS) remains unknown, continuing controversies and proposals arise about the preferential therapeutic strategy. In a large number of cases, the symptomatic therapy, according to the principal complaint of the patient, may represent the treatment of choice.

In this respect the combination of cyproterone acetate (CPA) and ethinyl oestradiol (EE); has been used to treat menstrual irregularities and androgenic clinical manifestations in PCOS women who were not interested in conceiving. The suppression of gonadotropin secretion and androgen production from ovaries and adrenal glands, the stimulation of sex-hormone binding globulin production along with the inhibition of peripheral androgen receptors are thought to account for the ability of these drugs to ameliorate hirsutism, acne and menstrual irregularities in women with PCOS ⁽⁵⁾.

The objective of the present study was to evaluate the effect of administration of CPA/EE combination (Diane 35) on the menstrual regulation, endocrine and ultrasonographic profile in women with polycystic ovary syndrome.

Patients and Methods

We enrolled 17 single women with PCOS (age range 18-45 years) attending our private clinic. All women had spontaneous onset of puberty and normal sexual development but had menstrual irregularity (oligomenorrhoea or amenorrhoea). None of them had taken medications known to effect menstrual pattern for at least 3 months before the study. PCOS was diagnosed on the basis of clinical findings (hirsutism, presence of amenorrhoea or oligomenorrhoea, and/or acne), plasma testosterone level at the upper limit or above the normal range 0.6-2.0 nmol/L and the presence of bilaterally normal or enlarged ovaries containing at least 7-10 microcysts (<5mm in diameter) on ultrasound examination ^(6, 7).

The menstrual patterns were defined according to Von Hooft et al⁽⁸⁾, regular cycles, length of cycle between (22 and 41 days); irregular cycle: oligo menorrhoea, length of between (42-180 days), poly menorrhoea, length of cycle (21 days or less); amenorrhoea: absence of menstruation for (180 days or more). Two or more such irregularities during the past year considered to be significant.

We questioned and evaluated all patients and analysed the actual menstrual cycle pattern at the time of the interview of each patient. At base line, during the early follicular phase of a spontaneous or induced (medroxy progesterone pills 10mg /day for 7 days) menstrual cycle (day 3-7). The patients were subjected to full gynaecological and medical examinations, all patients also underwent ultrasonographic examination, blood sample were collected to perform the basal hormonal assessment (testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin and estradiol).

The presence of a significant liver or renal impairment, neoplasm, and cardiovascular disease were considered exclusion criteria. A normal LH/FSH ratio was not considered an exclusion criterion ⁽⁸⁾. The first day of the following menstruation combination of 2mg cyproterone acetate (CPA) and 35µgm ethinyl oestradiol (EE) (Diane 35, Schering AG, Germany) was taken from (day 1-21) of the cycle followed by a pill free interval of 7 days, for 12 cycles.

During the study, chronically stabilised therapies not interfering with the parameter under evaluation were permitted, the use of anti-diabetic drugs was not allowed.

Patients were recommended not to modify their usual diet. After three cycles, on the third day of the menstrual bleeding, patients returned for another ultrasonographic examination and basal hormonal assay with assessment of menstrual cycle patterns, the patients returned to the clinic at the sixth and 12th cycles and repeated the basal study.

On each visit, compliance with treatment was checked and a subjective evaluation of the tolerability of the administered drug, the patients were also asked about incidental missed administration but all reported that they had correctly followed the scheduled treatment. To test if the relationship between Diane 35 and regularity of the cycle and endocrinological profile could be confounded by one of the following variables: age, weight loss, body mass index, and previous treatment with clomiphene citrate we performed a forward stepwise logistic regression analysis.

Trans abdominal pelvic ultrasound used before, and during the treatment. Ovarian volume was calculated by the simplified formula for ellipsoids: $0.5233 \times \text{length} \times \text{width} \times \text{depth}$ ⁽⁹⁾.

All values were expressed as mean $\pm$ SD. Paired t-test was used to compare hormone concentrations and ultrasonographic findings before and after treatment. The analysis of data of menstrual regulation done by Z-test (difference between 2 proportions). $P < 0.05$ was considered statistically significant.

Results

Twenty one women with PCOS were included in the study, and 17 patients completed the study therapy. Two patients were examined at baseline, but were excluded from the study after 2 months for lack of compliance. One woman excluded after 5 months because she travel abroad, and only one woman discontinued from the study after three cycles of treatment because of headache and gastric upset. This symptom resolved spontaneously within few weeks after the interruption of drug therapy. The treatment was well tolerated and correct intake of the drug was made by each of the remaining subjects, no serious adverse events were related to CPA/EE.

Table I: Depicts the variations in the endocrine features of the patients during treatment. A significant decrease in mean LH, FSH, testosterone levels as well as LH/FSH ratio were observed from the third cycle of drug assumption ($P < 0.01$ for 3rd, 6th and 12th cycle versus baseline).

Table I: changes in endocrine parameters during treatment with Diane-35 (mean $\pm$ SD)

Parameter	Baseline	Cycle 3	Cycle 6	Cycle 12
LH (IU/L)	14.4 $\pm$ 3.46	5.86 $\pm$ 2.27	4.6 $\pm$ 2.4	3.9 $\pm$ 2.2
FSH (IU/L)	6.7 $\pm$ 2.4	3.6 $\pm$ 1.46	3.2 $\pm$ 1.49	2.6 $\pm$ 1.24
Testosterone (nmol/L)	3.8 $\pm$ 1.68	2.9 $\pm$ 1.18	2.7 $\pm$ 1.14	2.5 $\pm$ 1.09
LH/FSH ratio	2.13	1.62	1.43	1.48

SD= Standard deviation. IU=international unit. nmol= nanomole. L=liter

Table II: Shows the ultrasound finding regarding ovarian morphological changes with Diane 35. It shows a marked decrease in ovarian size and volume ($P < 0.01$ for 3rd, 6th, 12th cycle versus basal), and a significant reduction in follicle size and number.

Table II: Shows the effect of Diane 35 on ovarian morphology.

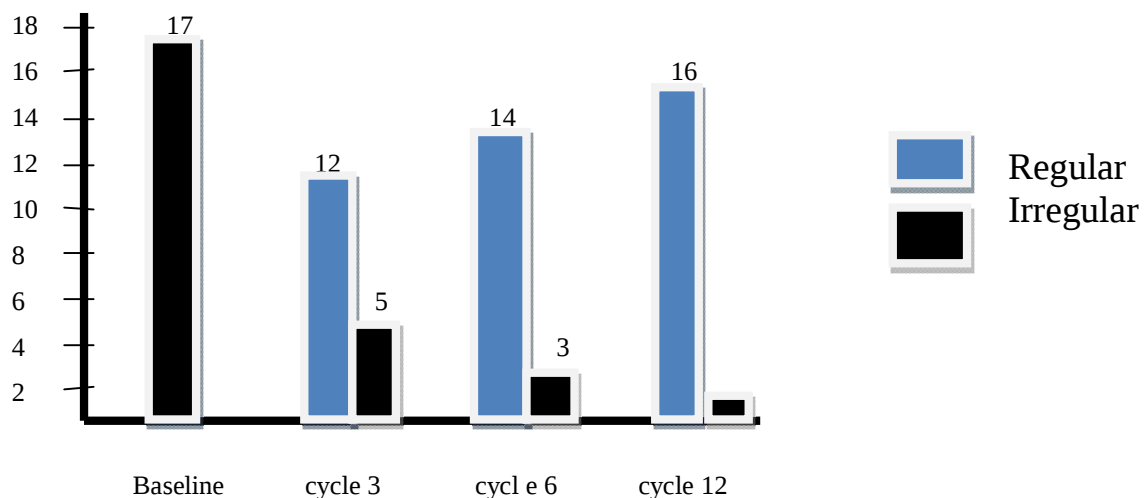
	Basal	Cycle 3	Cycle 6	Cycle 12
Mean ovarian volume (cm³)	18.2 ± 6.54	14.1 ± 4.72	11.6 ± 3.55	11.7 ± 3.1
% of women with >7 follicles per ovary	69.5	50.7	36.5	40.6

P value <0.01 compared with basal value

Cycle control was acceptable in the entire studied group, the duration of withdrawal menstrual bleeding ranged from (4-7 days), no case of amenorrhoea was observed. Break through bleeding and / or spotting occurred in 23% of patients during the first 3 cycle and 15% of patients reported these disturbances during at least one of the following cycle. (**Table III**)

(P<0.05 for 3rd, 6th, and 12th cycle versus baseline)

Table III: Changes in menstrual cycle pattern in patients with PCOS treated with Diane35.



Discussion

The present study demonstrates that CPA/EE pill administered for 12 consecutive cycles is able to significantly improve the clinical manifestations and endocrinological profile in patients with PCOS.

Several lines of evidence documented augmented LH pulse amplitude and frequency and increased expression of LH receptors in the ovaries of women with PCOS, so that many investigators consider these alterations to be central in the pathogenesis of the syndrome or at least of the hyperandrogenism that frequently characterizes it ⁽¹⁰⁾. In this respect, the significant decrease in serum LH observed in the present study appears particularly beneficial in PCOS patients showing elevated pre-treatment LH values. Our result are similar to those obtained by Golland and Elstein ⁽⁵⁾ and by Falsetti et al ⁽¹¹⁾, by

using the same drug, a significant decrease in plasma LH was obtained by these investigators after six treatment cycle and a significant trend for improvement was maintained until the 12th cycle, with no further variations after 60 cycle of Diane 35 administration.

The combination of Diane 35 has been demonstrated to directly reduce the production of testosterone and its precursors by an inhibition of the steroidogenic enzymatic activities ⁽¹¹⁾. Consistent with these data, a significant reduction in plasma testosterone levels was achieved in our patients from the third cycle of therapy.

The results of our study show that women with PCOS gain regular menstrual cycles with Diane 35 treatment. This evident effect of the drug on cycle length remains significant after correction for possible confounders such as the age, weight loss, body mass index, previous treatment with clomophine citrate using forward stepwise logistic regression analysis. Although cyproterone acetate if used alone there is usually disruption of the menstrual cycle ⁽¹³⁾, addition of ethinyl oestradiol is important to give good cycle control and to increase level of sex hormone binding globulin and thereby reduce free testosterone level ⁽¹⁴⁾

The treatment of enlarged poly cystic ovary by wedge resection can lead to regular menstrual cycle in PCOS patients ^(15,16). These observations led us to postulate that the enlarged antral follicle is an aetiological factor in PCOS and that a decrease in size of the ovaries and follicles leads to restoration of the functional balance for regular ovulatory cycle in the polycystic ovary. In our study a significant decrease in the size and volume of ovaries, reduction in the number of follicles per ovary started on 3rd months of treatment onward, this is in agreement with a study done by prelevic GM ⁽¹⁷⁾.

In conclusion treatment of women with polycystic ovary syndrome with Diane 35 for one year resulted in remarkable benefits with regard to hormonal, clinical and ultrasonographic profile of these patients.

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