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USE OF CYPROTERONE ACETATE (CPA) IN THE TREATMENT OF ACNE, HIRSUTISM AND VIRILISM

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SUMMARY

Cyproterone acetate, being both an antiandrogen and a progestogen, must be administered in women together with an oral estrogen in a "reverse sequential regime" to ensure cyclic withdrawal bleedings and to preclude conception. Such a regime consisting of the oral intake of 100 mg cyproterone acetate from day 5 to 14 and 50 μg ethinyl estradiol from day 5 to 25 of the cycle has been applied to over 600 patients, at 5 German centres, of whom about one third have been under the care of the author's group. Acne and seborrhoea are the symptoms which respond first and best with an almost 100% success rate after 3 months of medication. Usually, 6–9 months are necessary to improve hirsutism or even make it disappear in 60 to 80% of the subjects. The rest of the patients failed to respond or showed only poor improvement. Alopecia due to androgen overproduction was reduced only in about 50% of the individuals after a one-year treatment period. Following termination of the medication, the various symptoms of virilism reappeared more or less quickly and markedly in the majority of the patients unless they are placed on oral contraceptives containing a derivative of 17-acetoxyprogesterone. Side effects are comparable to those observed in oral contraception except for tiredness, lassitude and loss of libido which are seen more often. On the basis of hormonal analyses in blood and urine, it is suggested that the newly developed treatment acts both by competition with the androgens at the receptor sites and by lowering the ovarian androgen biosynthesis. Also, ovulation is reliably suppressed.

I. INTRODUCTION

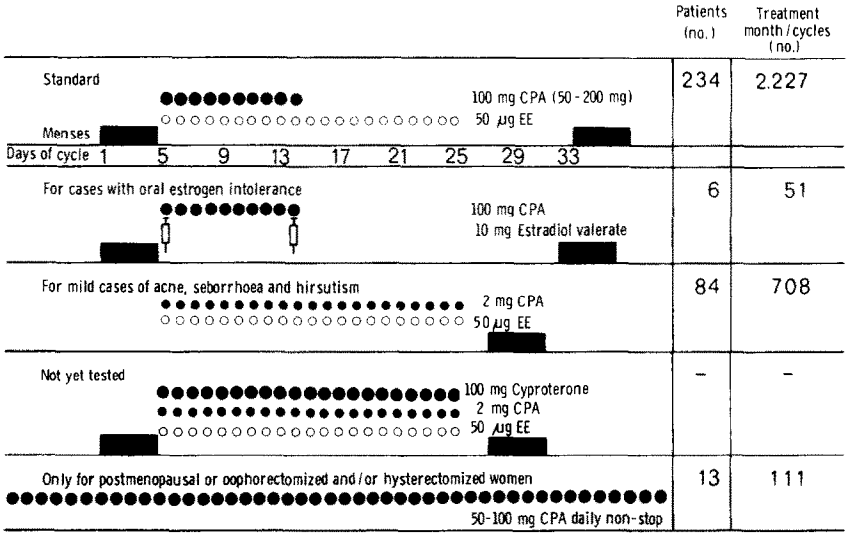
Of the many compounds with antiandrogenic potency which have been discovered in recent years only a few have progressed as far as clinical tests in man. Among these, only cyproterone acetate (CPA) (6-chloro-1α,2α-methylene-4,6-pregnadien-17α-ol-3,10-dione) has been investigated on a large scale in women with hirsuitism and acne. Like chlormadinone acetate, its parent compound, CPA is also a strong progestogen with the endometrial transformation dose of both drugs being between 20 and 30 mg. However, CPA is a stronger antiandrogen in animal tests than chlormadinone acetate. Both compounds also have antigonadotrophic properties but these appear to be ill-defined.

To take full therapeutic advantage of its antiandrogenicity, CPA must be administered in doses per month that are 30 times the physiological equivalent of progesterone production in the cycle. CPA, although the most useful compound available in this field at the moment, cannot be considered therefore an ideal antiandrogen, all the more as some of the side effects may be related to the progestational overdosage rather than to the administered antiandrogenic activity. From the clinical viewpoint three further aspects deserve interest. Firstly, CPA is only poorly absorbed, only 5–30% of the dose being absorbed, the proportion decreasing with increasing dosages [1, 2]. Secondly, CPA is markedly stored in the human body, preferentially in the adipose tissue, which leads to a marked depot effect when higher doses are administered. At the low contraceptive dosages, of 2–5 mg/day, this phenomenon is without clinical relevance. It should finally be mentioned that in numerous animal experiments, CPA has been shown to prevent the masculinization of male fetuses when given to the mother at the critical time of pregnancy. Special care must, therefore, be taken to avoid CPA medication at any time in pregnant women since the possibility of intersexual malformations cannot be ruled out.

II. REGIMES OF CPA APPLICABLE IN WOMEN

With these considerations in mind, in 1968 a special regime with CPA and ethinyl estradiol (EE) was developed which ensures cyclic withdrawal bleedings and precludes conceptions [3]. This standard regime consists of 100 mg CPA given daily from day 5 until day 14 together with 50 μg EE administered daily from day 5 until day 25 of the cycle (Table 1, first section). Even with this "reversed sequential" regime, menses-like bleedings do not occur, on the average, before the third till sixth day after termination of drug intake. In obese women, this interval usually is longer and may be up to 10 days; in this case the phase of combined CPA/EE administration should be reduced to 9 or 8 days. Only rarely, it may become feasible to increase the daily CPA dosage up to 200 mg or to decrease the dosage to 50 mg, but in

Table 1. Possible types of CPA regime in women



general 100 mg seems just the correct daily dose. If estrogens are not tolerated orally, 10 mg of estradiol valerate instead of the oral EE may be administered intramuscularly on days 5 and 14 of the cycle without any change in the expected bleeding pattern and in the clinical tolerance (Table 1, second section).

In patients with very mild forms of acne, seborrhoea and hirsutism, an attempt with the low-dosage combined formula of 2 mg CPA + 50 μg EE from day 5 until day 25 of the cycle rather than an attempt with the standard regime is indicated (Table 1, third section). On the basis of our observations in 74 women with 642 treatment cycles we can say that this therapeutic measure is comparable to the classical combined contraceptive pill as far as the contraceptive safety, side effects and acceptability are concerned. It is our feeling, therefore, that this regime should become the preferential contraceptive hormonal method in all kinds of mildly virilized patients. Furthermore, this treatment is useful as a consecutive measure to the standard treatment after the final clinical result has been achieved.

Free cyproterone (CP) being, in contrast to its acetate, a pure antiandrogenic compound devoid of additional hormonal activities does not inhibit ovulation and fertility. If at all, it should be used only in addition to a reliable contraceptive measure. The combination of the just mentioned low-dosage combined contraceptive pill containing 2 mg CPA and 50 μg EE per tablet together with high amounts of free CP would fulfil this requirement (Table 1, fourth section). This treatment should give the same beneficial results as the standard regime with the advantage of no progestational overdosage being implicated. Attempts to persuade the producer to provide such a formula have failed so far.

CPA without the addition of an estrogen should only be administered in the absence of the uterus and/or of ovarian estrogen production, *i.e.* to hysterectomized or oophorectomized as well as to postmenopausal women; otherwise bleeding disturbances are inevitable. These types of patients are of minor clinical importance and pure CPA treatment therefore is exceptional. The vast majority of cases must be submitted to the cyclic regime as is seen from the numbers of treated women indicated on the right side of Table 1. In the following, the presentation will be confined to this high-dosage reverse sequential application of CPA and EE, subsequently referred to as standard regime (Table 1, first section).

III. CLINICAL RESULTS

A. *Case presentations*

To demonstrate the effectiveness of the CPA/EE standard regime, three examples of virilism each due to a different cause will be presented first.

The first case, a 39-year-old woman, underwent total adrenalectomy on the right side as well as a subtotal removal of the left adrenal for the not verified suspicion of an adrenal tumor or hyperplasia 4 yr previously. Gradually after surgery, hirsutism became worse and both urinary 17-oxosteroid and testosterone excretion increased. At laparoscopy the ovaries were found to be enlarged and the diagnosis of ovarian hirsutism was made. Figures 1 to 3 demonstrate the severe hirsutism before treatment and its reduction after 9 months of the CPA/EE standard regime. It goes without saying that in this and the following cases the photographs were made under identical conditions, unless otherwise stated. The therapeutic result was classified as excellent, except for the beard which made shaving at weekly intervals necessary, instead of shaving every second day during the pre-treatment phase. It is our general experience that hirsutism responds best if no mechanical removal of hair is routinely done: the more shaving or other kind of manipulation, the less the therapeutic success. After termination of the medication, the symptoms gradually

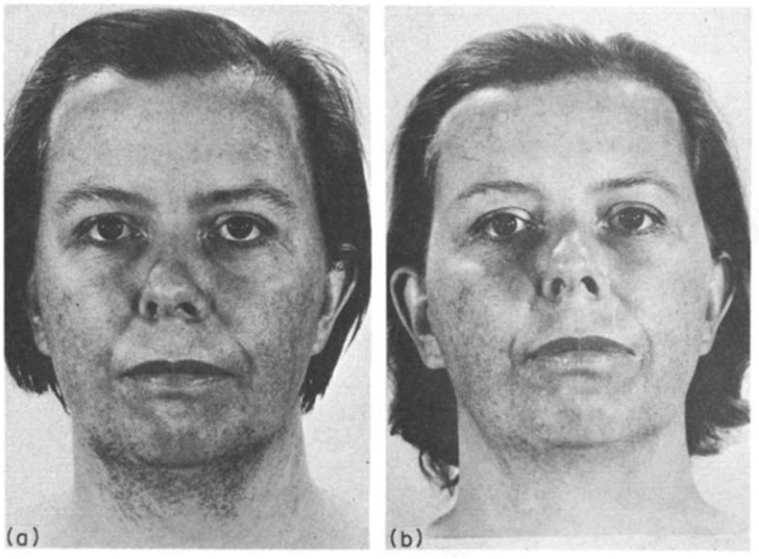


Fig. 1. 39-year-old patient with progressive ovarian hirsutism; subtotal adrenalectomy 4 yr previously. (a) Untreated. (b) After CPA/EE standard treatment for 10 months.

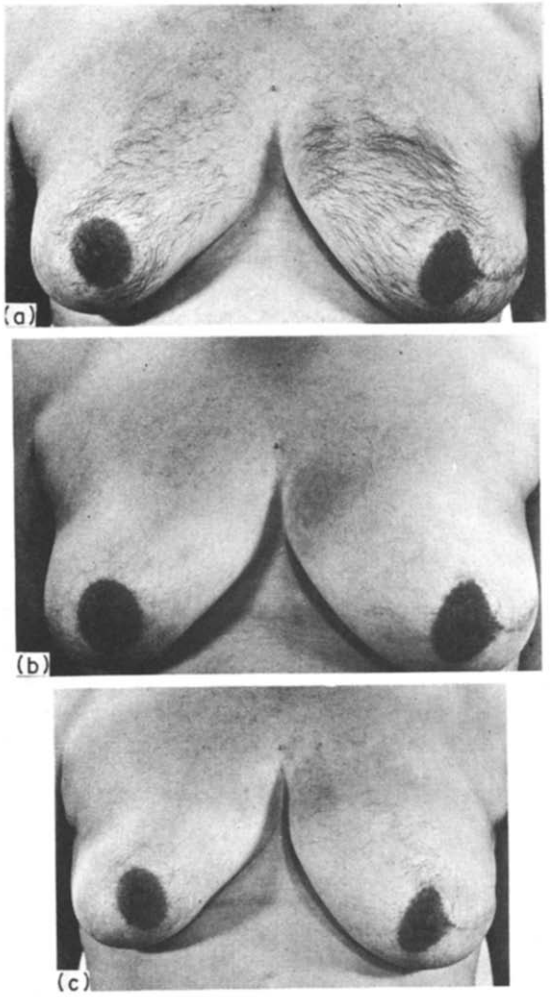


Fig. 2. (a) and (b) Same patient and therapeutical conditions as in Fig. 1. (c) 7 months after termination of treatment.

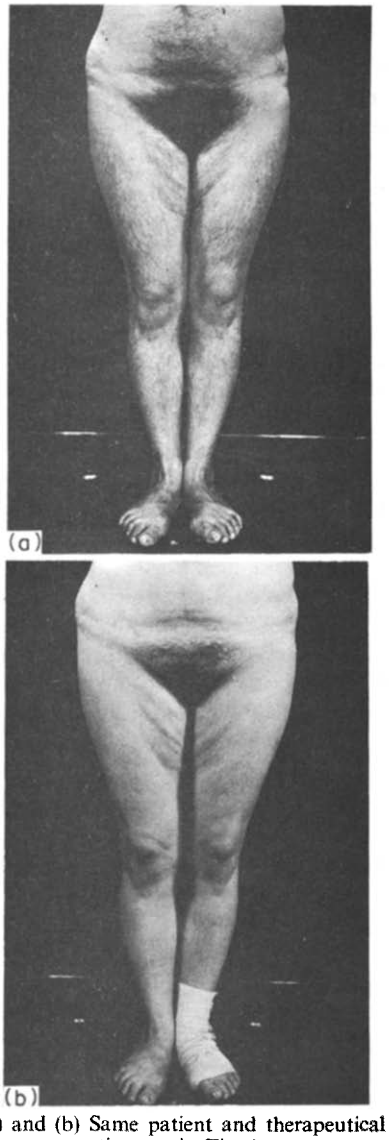


Fig. 3. (a) and (b) Same patient and therapeutical conditions as in Fig. 1.

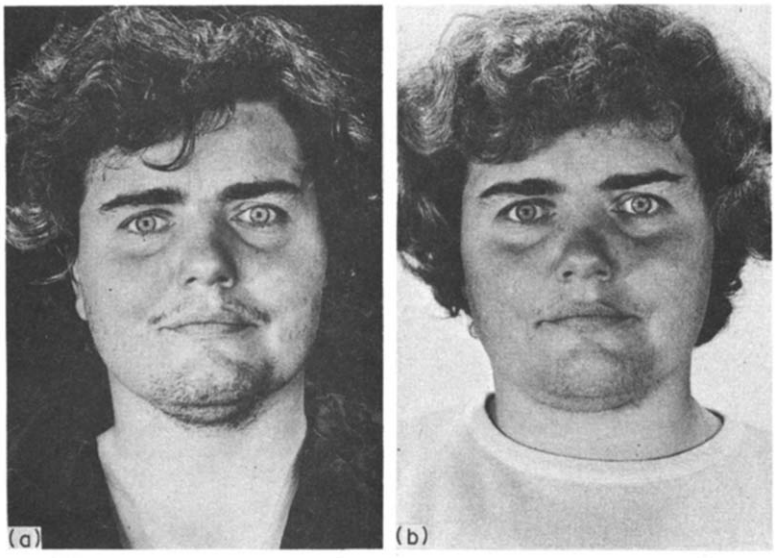


Fig. 4. 37-year-old patient with progressive adrenal hirsutism. (a) Untreated. (b) After CPA/EE standard treatment for 12 months.

reappeared in the course of 7 months, but did not reach anywhere near the pre-treatment intensity (Fig. 2c). Low-dosaged combined CPA/EE therapy then given for three months was without effect. The patient now is in the 10th month of her second CPA/EE standard treatment which again is giving excellent results.

The second case is a 37-year-old woman who presented herself with progressive hirsutism and a 17-oxosteroid excretion elevated to 26 mg/24 h. On the basis of thorough clinical examination the hirsutism and virilism was classified as purely adrenal in origin. Figures 4 and 5 demonstrate the excellent clinical response of the hirsutism to the CPA/EE standard regime after a period of 12 months treatment. Again facial hirsutism did not respond so well. Shaving intervals under treatment were 3–4 days instead of 2 days before the standard regime. Then, the patient was put on a megestrol acetate containing oral contraceptive. After 13 months of this medication a distinct reappearance of the hirsutism was seen with daily shavings becoming necessary (Fig. 5c). Low dosage combined CPA/EE medication given consecutively over 16 months did not improve the pattern of hirsutism. The patient is now back on the standard regime with good success.

The third patient was 22 years old when she presented first with a more stable kind of severe hirsutism predominating in the face in combination with hypertrichosis spread all over the body. The family history was indicative of an inherited abundance of hair growth. Clinical examination, including laparoscopy, revealed a normal appearance of the ovaries as well as normal results from the hormonal analyses, apart from an insignificant increase in the urinary 17-oxosteroid excretion from 4·8 to 6·7 mg/24 h and of the urinary testosterone excretion from 4·8 to 9·8 μg/24 h in the course of the dexamethasone-HCG test.

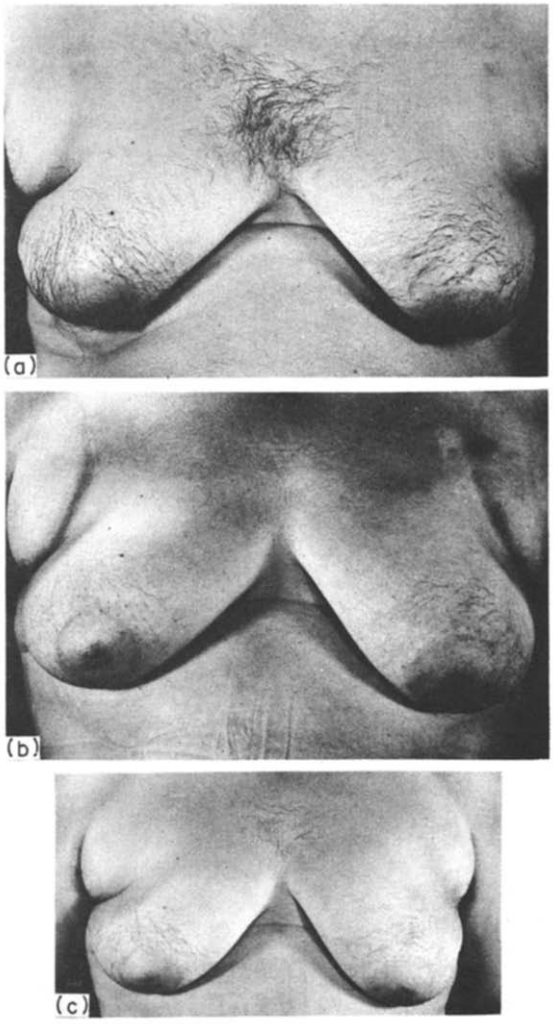


Fig. 5. (a) and (b) Same patient and therapeutical conditions as in Fig. 4. (c) After 13 months of intake of a megestrol acetate containing contraceptive.

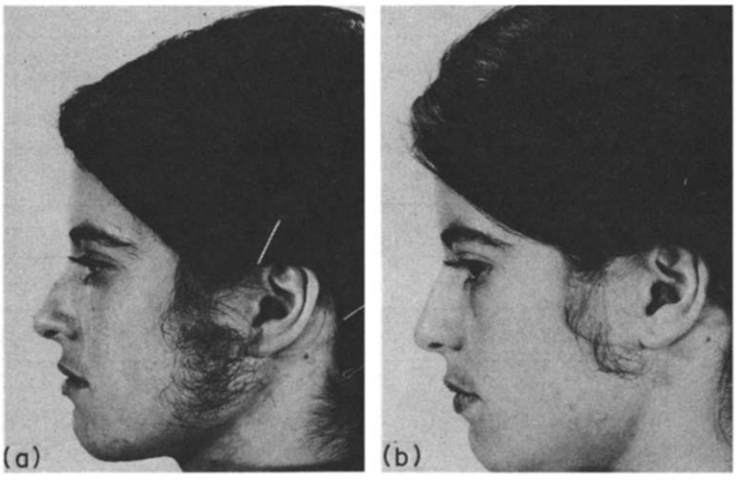


Fig. 6. 22-year-old patient with idiopathic hirsutism and hypertrichosis. (a) Untreated. (b) After CPA/EE standard treatment intermittently for 8 months.

The hirsutism was therefore classified as idiopathic. First clinical results after six months of CPA/EE standard regime, interruption for 3 months followed by two further treatment months are demonstrated in Fig. 6. After another 7 months of standard regime both the hirsutism and the hypertrichosis had disappeared totally. Even the removal of hair from the legs with wax was no longer necessary. Blond, sparse, fine intermediate-type hair was the only remnant of the previous hirsutism and hypertrichosis.

It is clear from these 3 presentations that hirsutism and virilism may respond favourably to CPA irrespective of its cause. In general, however, patients with idiopathic hirsutism are not as good candidates for this treatment as women with ovarian and/or adrenal hyperandrogenism.

B. *Statistical evaluation of data*

At a workshop of the last Congress of the German Society for Gynecology and Obstetrics in 1972, 602 standard treatments with CPA/EE as performed in 5 German university centers for gynecological endocrinology at Berlin, Düsseldorf, Frankfurt, Hamburg, and Ulm together were evaluated [4]. In the meantime, the clinical data of Dr. Bettendorf's group in Hamburg has increased to 241 patients treated in this way [5] while our own experience now comprises 234 cases, 193 of whom have been treated for 6 or more months over a total of 1885 cycles. Thus, enough clinical data have been accumulated to facilitate a well-grounded evaluation of the therapeutical efficacy and the side effects of this newly developed treatment.

From the combined data of the above mentioned workshop it is obvious that both acne and seborrhoea respond most rapidly and completely to the CPA/EE standard regime (Table 2). Hirsutism responds the next best, needing about 6–9 months of medication until a satisfactory clinical result is obtained; the success rate varied between 65 and 80% among the 5 centers. Finally, alopecia must often be treated for longer than a year before a satisfactory beneficial result is achieved. In our material only half of the cases with so-called androgenic alopecia were good responders to this treatment. From an increase of the CPA dosage in the standard regime only limited additional effectiveness could be achieved and this was counterbalanced by decreasing tolerance.

In a very preliminary follow-up study after termination of the treatment it was seen that about two thirds of the women experienced recurrence of their symptoms of virilization during the first 9 months. The beneficial therapeutic results were maintained, on the other hand, in two thirds of those patients who had been placed on a hormonal contraceptive containing a 17α-hydroxyprogesterone analogue as the progestational component (Table 3). If a second treatment course with the CPA/EE standard regime became

Table 2. Clinical results of the CPA/EE standard treatment in correlation with the duration of medication (Findings of 5 endocrinological centres for 602 patients)

		Distinct beneficial effect in % of all cases treated for indicated time				Total
Length of treatment (Months):		3	6	9	>9	
Hirsutism	Düsseldorf	65 %	55 %	77 %	80 %	102
	Frankfurt	--	--	28 %	--	11
	Hamburg	30 %	80 %	86 %	76 %	97
	Ulm	--	--	89 %	--	44
	Berlin	12 %	43 %	56 %	65 %	136
	Total	23 %	50 %	60 %	69 %	390
Acne	Düsseldorf	87 %	75 %	67 %	71 %	44
	Frankfurt	--	--	100 %	--	3
	Hamburg	86 %	82 %	100 %	100 %	42
	Ulm	--	--	--	100 %	15
	Berlin	61 %	89 %	97 %	97 %	71
	Total	68 %	87 %	95 %	96 %	175
Seborrhea	Düsseldorf	87 %	76 %	59 %	69 %	78
	Frankfurt	--	--	--	--	--
	Hamburg	80 %	100 %	100 %	100 %	18
	Ulm	--	--	--	100 %	1
	Berlin	63 %	86 %	94 %	94 %	64
	Total	69 %	84 %	87 %	89 %	160
Androgenic Alopecia	Düsseldorf	66 %	33 %	75 %	50 %	32
	Frankfurt	--	--	0	--	2
	Hamburg	17 %	25 %	0	100 %	15
	Ulm	--	--	--	50 %	6
	Berlin	7 %	14 %	23 %	40 %	44
	Total	19 %	16 %	26 %	45 %	99

Table 3. Follow-up of 76 patients after termination of the CPA/EE standard treatment

Consecutive treatment	Change in clinical Appearance in comparison with CPA/EE	Months after termination of CPA/EE medication				Total
		1 - 3	4 - 6	7 - 9	≥9	
None	none	6	4	3	2	15
	worse	11	6	2	6	25
Ovulation inhibitors with megestrol acetate or chlormadinon acetate as progestational component	none	3	11	3	8	25
	worse	5	5	-	1	11

necessary, the same or even better relief of the symptoms was obtained. For example, one of our highly virilized patients has been taking CPA therapy of various kinds since 1967 with short interruptions. Originally she needed the CPA/EE standard regime to achieve beneficial therapeutical effects, at present the standard regime with only half the CPA dosage is sufficient to obtain the same clinical results.

Tiredness often combined with lassitude, increase in body weight and loss of libido are the adverse reactions most often complained about during the CPA/EE standard regime (Table 4). While the former two symptoms are attributable to the progestational partial activity of CPA rather than to its antiandrogenic one, the opposite appears to be true for the loss of libido. As far as changes in body weight are concerned, increases have been recorded in 18·5% and decreases in 12% (Fig. 7). Such weight changes are less pronounced after 3 than after 6 months of the standard regime and are rarely excessive. Breast discomforts, *i.e.* most often tenderness of the mammae, also relatively often caused complaint. Mammography performed in 46 unselected patients before and during the CPA/EE standard regime did not reveal pathological changes occurring under the medication. The rare occurrence of thrombophlebitis and thrombosis causes concern. All the residual side effects are of minor importance and compare well in frequency and intensity with those known to occur during oral contraception. The drop-out rate for medical reasons in our material was 6·5%.

Table 4. Side effects under CPA/EE standard treatment (Findings of 5 endocrinological centers for 602 patients according to Breckwoldt, 1972)

Tiredness, lassitude	:	132	22,0 %
Increase in body weight	:	86	18,5 %
Loss of libido	:	60	10,0 %
Breast discomfort	:	55	9,2 %
Nausea	:	54	9,0 %
Headache	:	44	7,3 %
Depression	:	31	5,1 %
Irregular uterine bleeding	:	22	3,5 %
Sleep disturbance	:	22	3,5 %
Thrombophlebitis	:	6	1,0 %
Chloasma	:	5	0,9 %
Constipation	:	3	0,5 %
Thrombosis	:	1	0,15 %

IV. INFLUENCE OF THE ANTIANDROGEN TREATMENT ON THE ENDOCRINE SYSTEM

Figures 8–10 clearly show that the urinary excretion of testosterone, 17-oxosteroids, and total 17-hydroxysteroids, in decreasing order, is significantly reduced under the CPA/EE standard regime. Individually a wide scatter of responses is seen but the tendency to a greater drop in cases with elevated basal values is obvious both in absolute and relative terms.

If the absolute differences between the individual

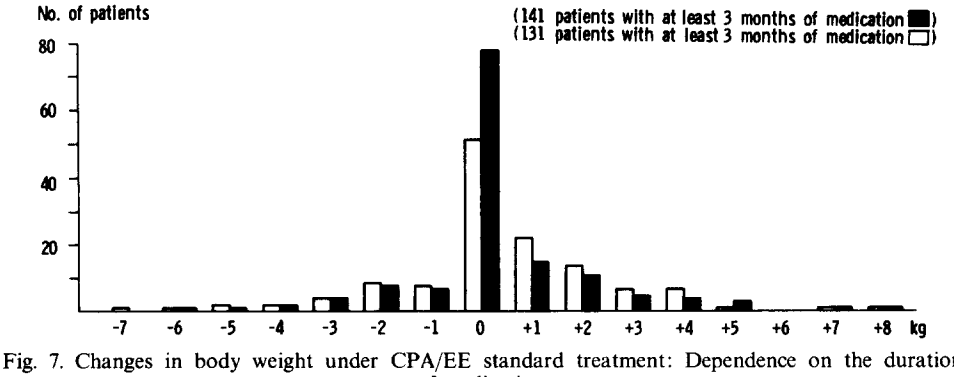


Fig. 7. Changes in body weight under CPA/EE standard treatment: Dependence on the duration of medication.

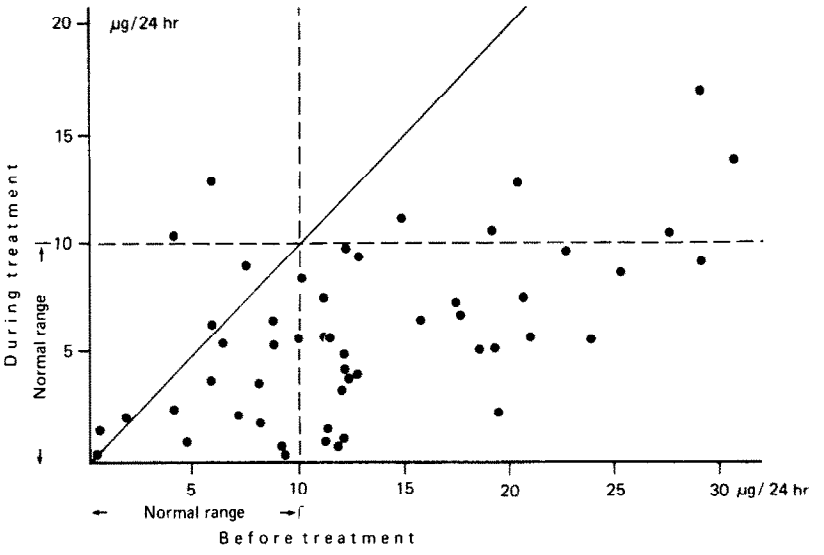


Fig. 8. Correlation between urinary testosterone excretion before and during CPA/EE standard treatment (52 patients).

basal and treatment values are plotted against the length of treatment, no obvious changes or trends in respect to the urinary 17-oxosteroid and total 17-hydroxysteroid excretion with increasing duration of the therapy are discernable (Figs. 11 and 12). There was a gradual drop in the urinary testosterone excretion up to 4–6 months of treatment followed by a subsequent increase which might be accidental due to the too small number of cases and needs further investigation (Fig. 13). It is of considerable interest that in none of the 3 analytical parameters tested, did the excretion values reach the pre-treatment levels after termination of the medication, thus pointing to a possible long-term effect of CPA on organs involved in the production of steroids. However, it should also be mentioned, that continuous administration of CPA without an estrogen to two adult individuals with congenital adrenogenital syndrome failed to prevent a gradual increase in the urinary excretion of 17-oxosteroids and total 17-hydroxysteroids up to almost pre-treatment values. This was accompanied by a recurrence of acne and an aggravation of hirsutism. An efficient suppressive effect of CPA on the hypothalamo-hypophysealadrenal axis appears therefore to be improbable [6].

As in the case of hormonal contraceptives, ovulation and subsequent corpus luteum formation is obviously reliably suppressed under the CPA/EE

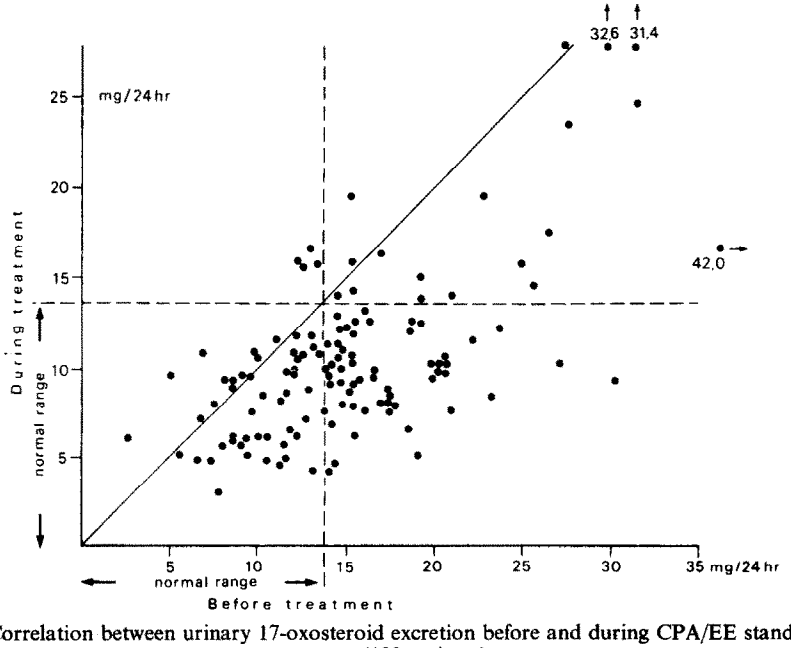


Fig. 9. Correlation between urinary 17-oxosteroid excretion before and during CPA/EE standard treatment (123 patients).

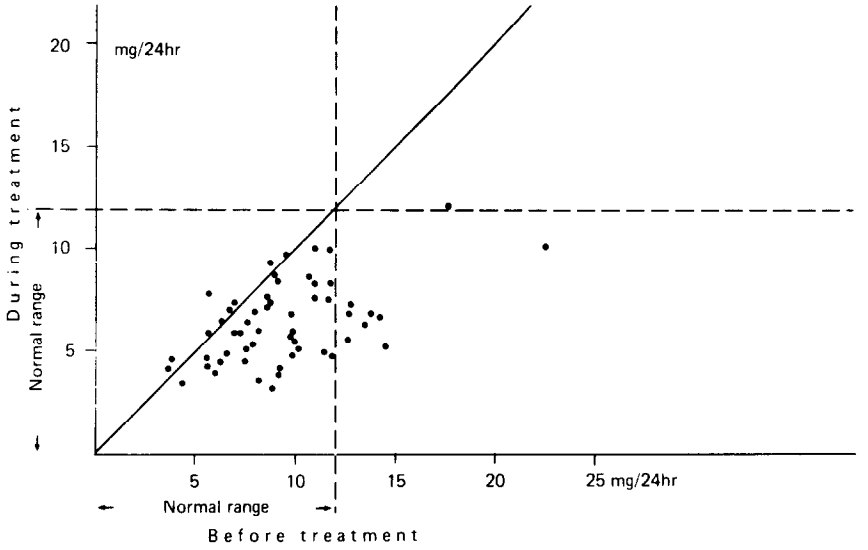


Fig. 10. Correlation between urinary 17-hydroxysteroid excretion before and during CPA/EE standard treatment (55 patients).

standard regime. This can be concluded from 33 urinary pregnanediol and 32 plasma progesterone determinations in the second half of cycles under treatment with CPA/EE (Figs. 14 and 15). All the results fell in the non-luteal range. As is to be expected, so far no pregnancy has been reported under this therapeutic regime. It should be mentioned here that there is a rapid recurrence of spontaneous menstrual cycles after termination of the CPA/EE treatment. Also, fertility is soon restored as may be concluded from 10 pregnancies after termination of the CPA intake. These mothers gave birth to 7 male infants who were free from intersexual malformations.

V. CONCLUSIONS

In conclusion, CPA possesses sufficient antiandrogenic activity to be successfully used in virilized women. In the form of the reversed sequential formula, it is distinctly superior to other hormonal measures for the treatment of all kinds of virilization except the congenital adrenogenital syndrome which

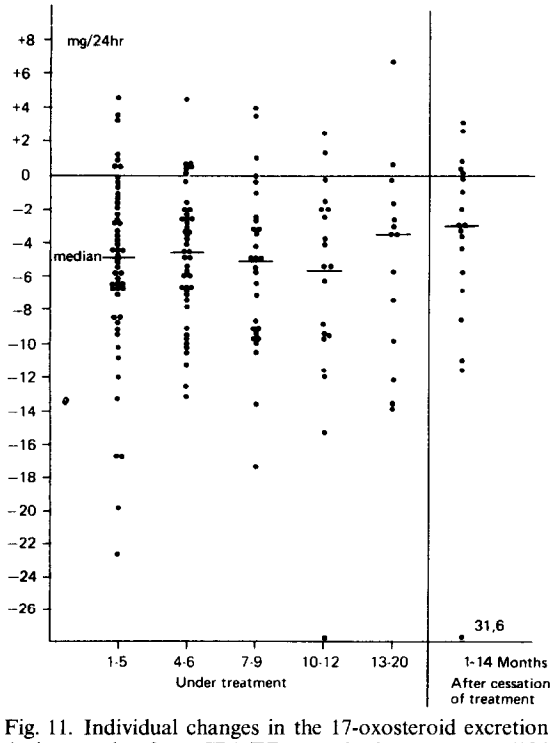


Fig. 11. Individual changes in the 17-oxosteroid excretion during and after CPA/EE standard treatment (124 patients).

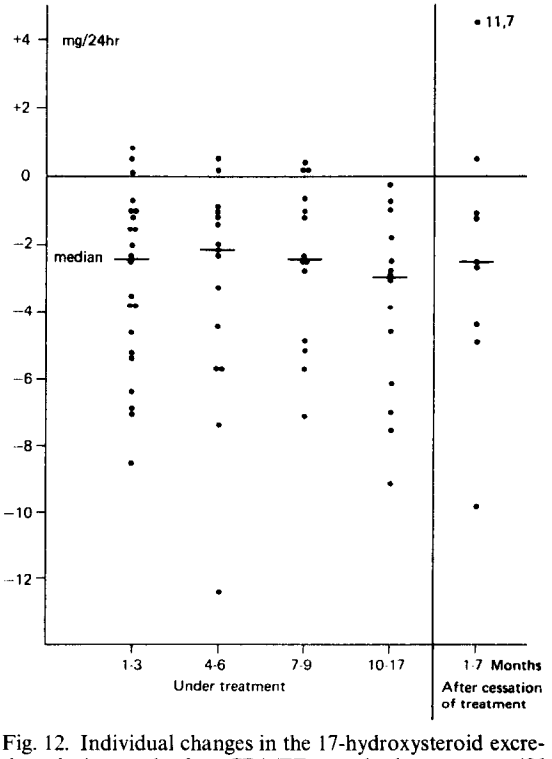


Fig. 12. Individual changes in the 17-hydroxysteroid excretion during and after CPA/EE standard treatment (56 patients).

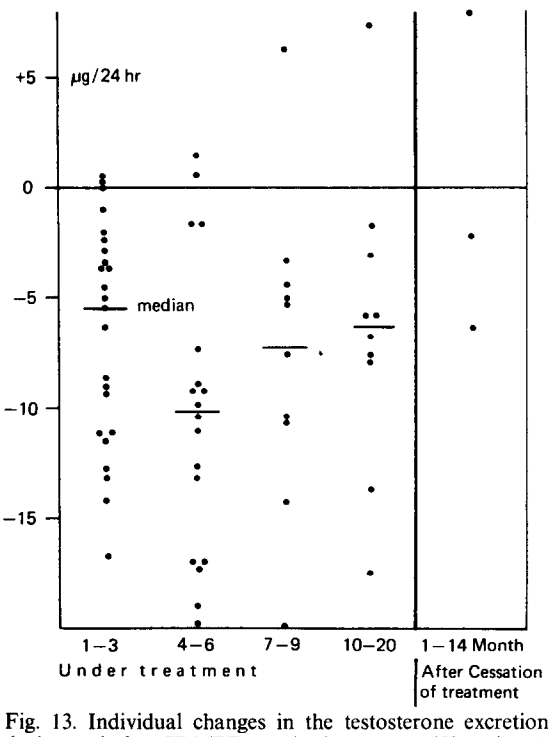


Fig. 13. Individual changes in the testosterone excretion during and after CPA/EE standard treatment (52 patients).

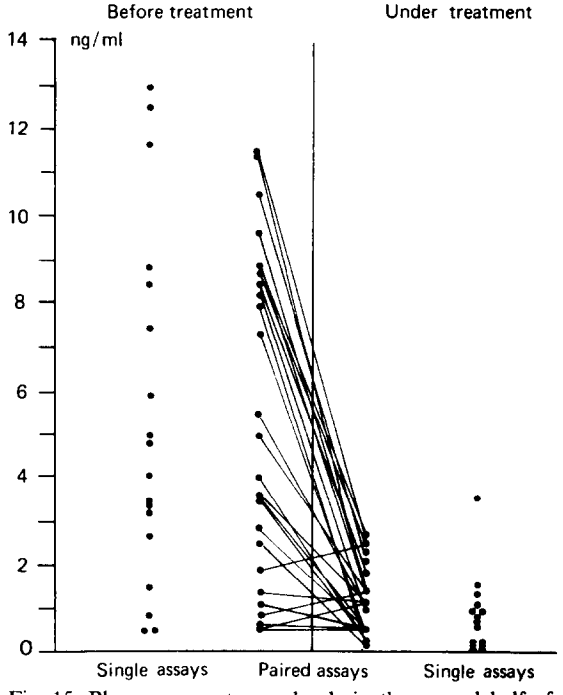


Fig. 15. Plasma progesterone levels in the second half of the cycle before and during CPA/EE standard treatment (57 patients).

is better handled with corticoids (Table 5). It remains open to explanation why beneficial results are achieved in the case of acne and seborrhoea at an almost 100% rate whereas patients with hirsutism and alopecia are more or less resistent to this treatment with a 20–35% or 40–50% failure rate, respectively. The poor absorption rate of CPA could be of therapeutical relevance in this respect. Adverse reactions like tiredness, lassitude, and increase in body weight are possibly due to the enormous overdose of progestational activity in the formula which is necessary to take full advantage of the antiandrogenicity of CPA. Although the CPA/EE standard regime is otherwise well tolerated, one should therefore continue to look for better balanced preparations with no depot properties. Combination of pure cyproterone with the low dosage CPA/EE contraceptive formula might be of advantage in this respect (Table 1, fourth section).

The distinct diminution in the urinary excretion of both testosterone and 17-oxosteroids points to the possibility that the CPA/EE standard treatment not only displaces androgens from the receptor site but also decreases androgen production. Additional parameters will be checked to investigate this assumption.

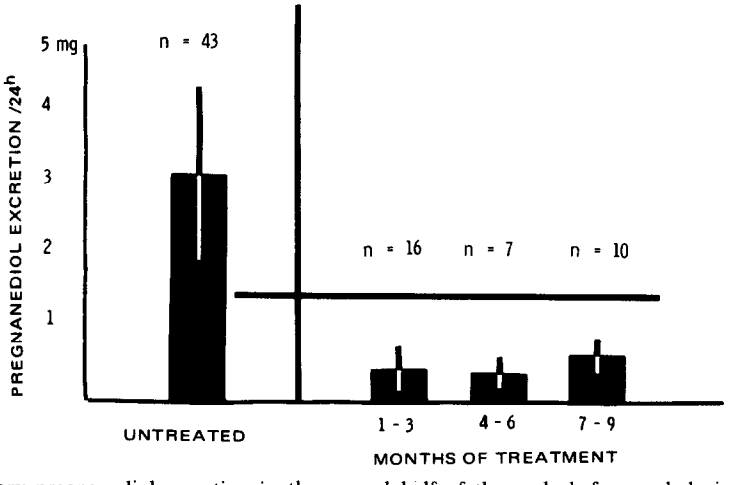


Fig. 14. Urinary pregnanediol excretion in the second half of the cycle before and during CPA/EE standard treatment (43 patients).

Table 5. Comparison between the clinical results of 4 hormonal types of treatment of hirsutism (patients with congenital adrenogenital syndrome not included). The vast majority of women underwent at least two types of treatment subsequently

Drug	No. of Pat.	Average duration of treatment (months)	Effect of treatment on hirsutism (No. of patients)			
			worse	unchanged	slightly better	greatly better, cured
Corticoids	26	8,5	8	15	3	--
Ovulation inhibitors	26	8,1	4	16	6	--
Cyproterone	14	5,4	--	7	7	--
Cyproterone acetate, CPA/EE standard regime	52	7,9	--	13	31	8

Acknowledgements—Cyproterone acetate together with and without ethinyl estradiol was kindly supplied in three formulas (SH 81041, SHB 209 AB and SH 80714) from Schering AG, Berlin. The permission of Drs. G. Bettendorf (Hamburg), M. Breckwoldt (Freiburg i.Br.), Ch. Lauritzen (Ulm), H. Schmidt-Elmendorff (Düsseldorf) and H. D. Taubert (Frankfurt) for using their data here is thankfully acknowledged.

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