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Preliminary Studies on Metabolic Effects of a Continuous-Dose, Progestogen-Only, Oral Contraceptive

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Summary. A continuous daily dose of 0·3 mg norethisterone acetate was administered as contraceptive to 321 women for a total of 1857 cycles. The method had a failure rate equivalent to nine pregnancies per 100 women-year of use. Cycles during treatment were irregular, but otherwise few side-effects were reported. The preparation had small, but probably significant effects on urinary steroid excretions, and from pregnanediol estimations it seemed likely that ovulation was inhibited in some patients. Most other biochemical parameters examined on blood and urine samples were little altered, but serum iron and iron-binding capacity were significantly elevated.

Résumé. Une dose quotidienne continue de 0,3 mg d'acétate de nor-thistérone a été administrée comme contraceptif à 321 femmes sur un ensemble de 1.875 cycles. La méthode a présenté un taux d'échec équivalant à 9 grossesses pour cent femmes-année d'emploi. Pendant le traitement les cycles ont été irréguliers mais par ailleurs on n'a noté que peu d'effects secondaires. La préparation a exercé une influence mineure mais probablement significative sur les excrétions urinaires de stéroides et selon les estimations de pregnanediol l'ovulation a été vraisemblablement inhibée chez quelques sujets. La plupart des autres paramètres biochimiques examinés dans les spécimens de sang et d'urine étaient peu changés, mais le fer sérique et la capacité de saturation de la sidérophilin étaient considérablement élevés.

INTRODUCTION

Three types of steroid oral contraceptive have been developed and made commercially available (Haller, 1969). These include:

(a) Progestogen/oestrogen combinations in which each tablet of the preparation contains both hormones in a fixed dose: these are taken for 20 or 21 days with a tablet-free interval of 7 days before the next course.

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(b) Sequential or serial preparations consisting of a course of an oestrogen alone followed by a course of progestogen plus oestrogen: these also have a tablet-free interval.

(c) Progestogen-only products, in which the preparation contains only one hormone in a fixed dose and is taken continuously without a break.

The latter products have been colloquially named 'mini-pills'. They are relatively new and studies have been published on products based on only a few compounds; notably chlormadinone acetate (0·5 mg daily) (Christie & Moore-Robinson, 1969); megestrol acetate (0·5 mg daily) (Mason *et al.*, 1967; Leusden, 1969) and norgestrel (0·05–0·075 mg daily) (Foss 1969, Foss *et al.*, 1969; Tyler, 1968).

The only commercially available 'mini-pills', which were based on chlormadinone acetate, were withdrawn from sale in February 1970 following reports of benign breast lumps in dogs during chronic toxicity trials. This evidence is now regarded as suspect and permission has been requested to re-market the product.

The present study is an investigation of a mini-pill where the active ingredient was norethisterone acetate (0·3 mg daily).

Mini-pills were introduced as an attempt to produce a method of oral contraception that is as reliable as alternatives, but free from the serious side-effects that undoubtedly accompany the currently available products (Haller, 1969).

The mode of action of both the combined and sequential types of oral contraceptive is thought to involve primarily the suppression of pituitary secretion of gonadotrophins (Loraine & Bell, 1968). This leads to inhibition of ovulation. Secondary modes of action are effects on the uterine endometrium and on the mucus of the cervical canal. In contrast to these effects, studies on the mode of action of mini-pills have shown that they do not consistently inhibit ovulation and urinary hormone excretions are often in the normal range (Martinez-Manautou, *et al.*, 1967).

The only previously published studies with norethisterone acetate, without added oestrogen, are at a daily dose level many times that of the present preparation and administered for gynaecological indications other than contraception (Brown, Fotherby & Loraine, 1962; McCormick, Carlsborg & Gemzell, 1968).

METHODS AND MATERIALS

1. *Product*

Norethisterone acetate is an orally active progestogen. In the micronized form present in the product used it is almost five times as active (progestational action) as in the usually available particle size. Norethisterone acetate is 17α-ethinyl-19-nortestosterone acetate (17-α-ethinyl-17β-acetoxy-estr-4-en-3-one). It is a white crystalline powder, m.p. 163°C, $(\alpha)_D^{20} = -19{\cdot}5°$. The acute oral toxicity (LD_{50}) in mice is 1·4g/kg.

The progestogen was contained in white, lustrous, sugar-coated tablets that were packaged in a 28-day calendar pack.

2. *Selection of patients*

Women were recruited through family planning clinics. Only women of confirmed fertility, which for the purpose of this trial was defined as at least one pregnancy within the last 5 years, were admitted. Age limits of 18–40 years at the beginning of the trial were arbitrarily selected.

Before entry into the trial and beginning tablets, detailed medical, gynaecological and obstetric histories were taken. Every trial participant received complete pelvic and breast examinations, a cervical smear was taken and pregnancy eliminated by means of a urine slide test. Weight and blood pressure were recorded.

The following women were specifically excluded from the investigations:

(a) those with acute or chronic diseases of the gastro-intestinal tract or liver,

(b) those requiring hormonal therapy of any type for any indication other than contraception,

(c) those with a positive or doubtful Papanicolaou smear,

(d) those with any suspicion of breast diseases of any kind.

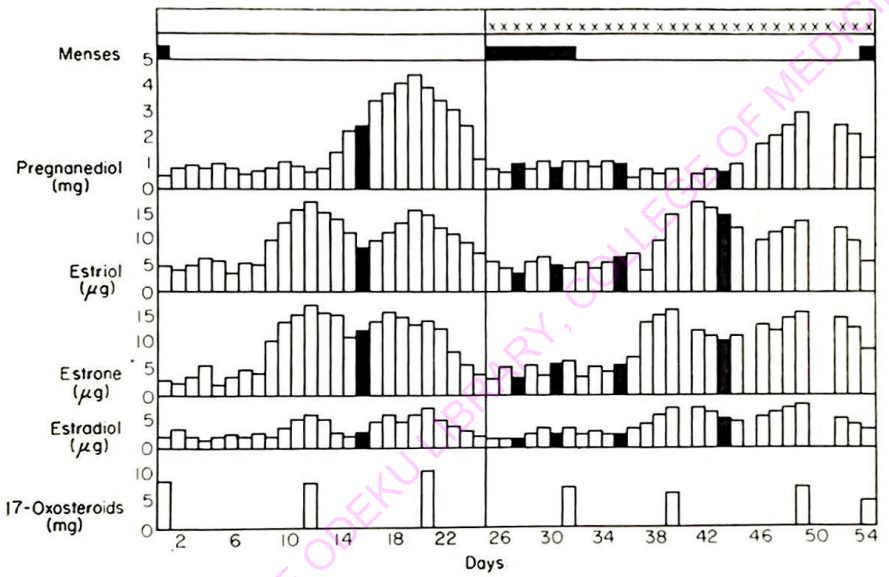

FIG. 1. Urinary steriods: Patient B.

The trial on each patient lasted for 6 months or until tablets had to be stopped for medical or other reasons.

All patients were particularly instructed on the importance of regular tablet taking; especially those who had at some time previous received other types of oral contraceptive. It was stressed that one tablet is taken each day, regularly and continuously, without interruption: even during bleeding. Patients were specifically asked to take the tablets at the same time each day and three different times were recommended; namely, before breakfast, before lunch, or last thing at night.

3. *Side-effect reports*

At the first attendance each patient was told about the nature of oral contraception and of the possible side-effects which may be experienced. She was informed that most of these are rare and all were unlikely on the low dose preparation being used in this trial. The patient was informed that the product was a trial preparation and consequently that the risk of pregnancy was higher than on tested products.

On subsequent monthly visits, a single enquiry into side-effects was sufficient and specific enquires on each possible side-effect were not made. Detailed enquires were made, however, on cycle length and irregularity. Regular cycles were defined as those falling between the arbitrary values of 24 and 32 days.

With regard to blood pressure, hypertension was defined as consisting of the mean systolic pressure above 155 mm or diastolic pressure above 100 mmHg. Hypotension was considered as a systolic pressure below 90 mm or diastolic pressure below 50 mmHg.

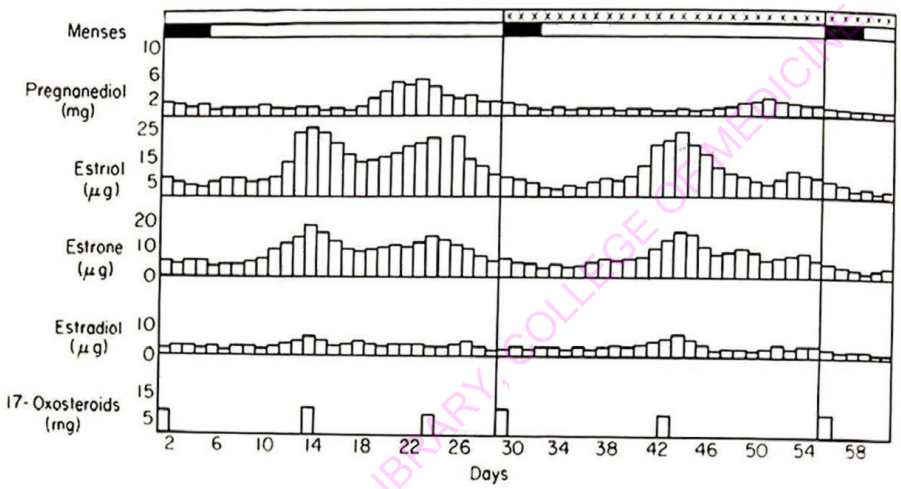

FIG. 2. Urinary steroids: Patient L.

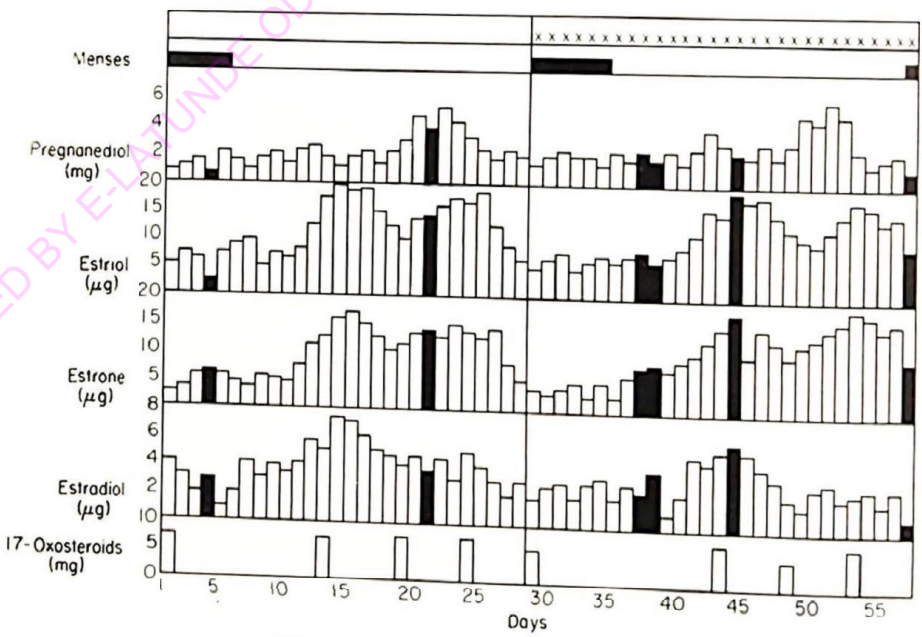

FIG. 3. Urinary steroids: Patient R.

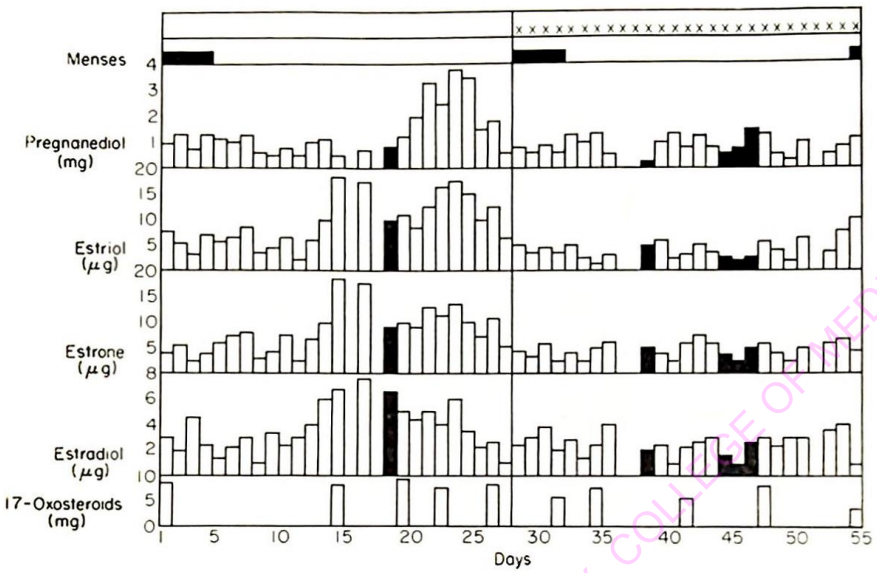

FIG. 4. Urinary steroids: Patient S.

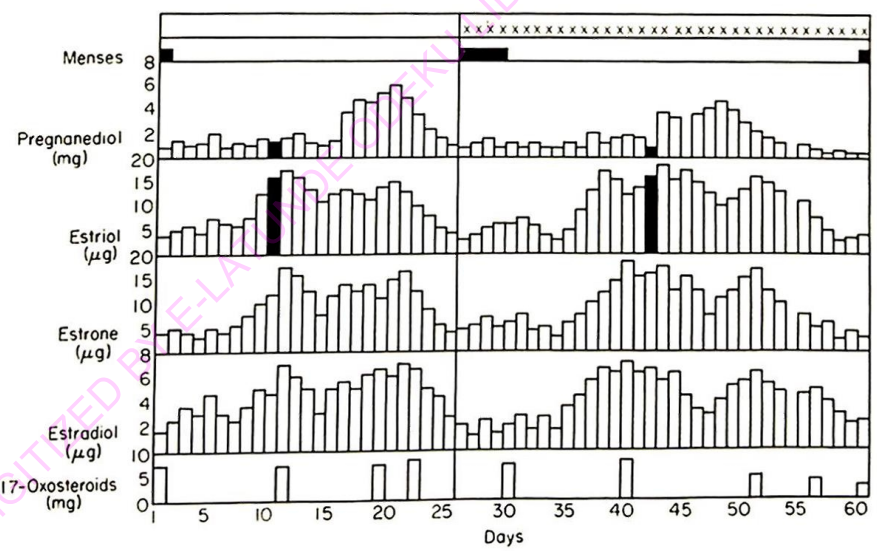

FIG. 5. Urinary steroids: Patient So.

4. *Removing the patients from the trial*

Treatment was stopped for any of the following reasons: (a) pregnancy, (b) severe side-effect, (c) the patient missing consultations or check-ups, (d) the patient failing to co-operate in providing details, (e) the patient failing to take the tablets regularly.

5. *Metabolic studies*

Five young married women (patients B, L, R, S and So) were investigated in detail. Three of the five had previously received combined oral contraceptives but all had discontinued at least 3 months prior to the investigations.

Each patient was asked to collect 24-hr urine samples for two complete menstrual cycles. The first cycle, which was calculated from the first day of bleeding, was without treatment. During the second cycle tablets were taken daily from the first day of bleeding (Figs. 1–5).

Methods of assay for individual urine and blood components are set out in Table 1. Occasional urea clearance and glucose tolerance tests (Exton-Rose) were conducted.

TABLE 1. Investigative methods

Sample	Investigation	Method
Urine	Pregnanediol	Klopper *et al.*, 1955
	Oestriol	Brown, 1955
	Oestrone	Brown, 1955
	Oestradiol	Brown, 1955
	17-Oxosteroids	Vestergaard, 1951
	Creatinine	Henry, 1966 (p. 292)
	Glucose	Henry, 1966 (p. 653)
Blood	Transaminases	Henry, 1966 (p. 513, 519)
	Glucose	Henry, 1966 (p. 648)
	Creatinine	Henry, 1966 (p. 294)
	Urea	Henry, 1966 (p. 267)
	Magnesium	Henry, 1966 (p. 381)
	Phosphorus (inorganic)	Delsal & Manhouri, 1958
	Iron	Kok & Wild, 1960
	Haemoglobin	Henry, 1966 (p. 742)
	Iron-binding capacity	Henry, 1966 (p. 391)
	Copper	Henry, 1966 (p. 397)
	Ceruloplasmin	Henry, *et al.*, 1960

RESULTS

1. *Contraceptive efficacy*

In all, the total number of monthly cycles which were recorded was 1857, which is equivalent to 154 woman-years of use. In all, fourteen patients became pregnant. This gives an approximate method failure of nine per 100 woman-years.

Unfortunately, in studies of the present type, it is extremely difficult to distinguish between product and patient failure and in most of the pregnancies the woman denied missing tablets. The distribution of pregnancies in terms of months of use of the product was

as follows: two in month 1, two in month 2, four in month 3, three in month 4, one in month 5, one in month 6, one in month 7. These results indicate that duration of use does not particularly correlate with failure.

2. *Side-effects*

An analysis of the reported incidence of particular side-effects is set out in Table 2.

TABLE 2. Side-effects with 300 μg daily norethisterone acetate

	Patients reporting side-effect (%)						
	Pretreatment cycle	Cycle No.					
Side-effect		1	2	3	4	5	6
Depression	15	12	10	8	8	11	10
Nervousness	13	9	8	5	6	7	8
Libido decreased	5	7	7	10	7	9	5
Libido increased	0	7	5	7	5	7	5
Nausea	2	12	5	2	3	3	2
Vomiting	0	4	2	2	2	0	0
Dizziness	5	8	5	4	6	4	2
Headaches	24	25	12	13	15	15	10
Dysmenorrhea	21	19	18	16	20	18	14
Menorrhagia	12	14	12	5	7	5	8
Breast tension	14	19	13	13	14	13	12

Depression and nervousness were frequently reported by some patients but no particular effect of the product on these conditions can be seen. The effect on libido was small but there seems to be a tendency for a decrease in the majority of subjects, although a few individuals experienced a constant increase over the first six cycles. Nausea and vomiting increased in the first few cycles, but thereafter declined. Only a few patients experienced dizziness and the effect on headaches was not particularly striking. Heavy periods were reported quite frequently, but were also a feature of the control cycle and appeared to decrease somewhat with duration of treatment. Spotting also increased in the first 3 months but again subsided to a relatively low figure.

Analysis of reported cycle lengths for the first 6 months of treatment is given in Fig. 6. There is clearly an effect of the product which alters cycle length, some patients showing extremely long cycles and others very short ones. This tendency appears to be maintained throughout the duration of the trial and the effect is probably the most striking of all the changes noted in the treated patients.

3. *Metabolic results*

Results of the various studies are set out in the following figures and tables. Figures 2–6 show the results of urine steroid hormones assayed for each of five patients individually. In these histograms a darkened area indicates a day when urine collection was incomplete. A summary of findings on serum transaminases are shown in Table 3 while Table 4 shows the

results of creatinine clearance tests. A breakdown of findings on various mineral constituents of the blood samples is shown in Table 5.

Glucose-tolerance tests were normal at all times.

TABLE 3. Effect of 300 μg norethisterone acetate on serum transaminases

Period of treatment	Mean* serum transaminases (i.u./l)	
	Glutamate-oxalacetate	Glutamate-pyruvate
0	9·5	6·5
1	10·5	6·0
3	8·0	7·5
6	9·0	6·0

* of 5 patients.

TABLE 4. Effect of 300 μg norethisterone acetate on creatinine clearances

Patient	Value after 3 months treatment (1/24 hr/1·73 m²)
So	170
H	165
R	168
S	162
L	170

Normal range, 150–180.

TABLE 5. Mineral constituents of serum

Substance	Mean serum concentration (units ± SD/100 ml)	
	Control	After 3 months treatment
Phosphorus (inorganic) (mg)	3·4 ± 0·2	3·3 ± 0·3
Magnesium (mg)	2·5 ± 0·2	2·3 ± 0·2
Iron (μg)	89 ± 25	115 ± 21
Iron-binding capacity (mg)	358 ± 38	428 ± 59
Copper (μg)	121 ± 15	128 ± 20
Ceruloplasmin (μg)	31 ± 4	33 ± 6

CONCLUSIONS

The contraceptive efficacy of 0·3 mg daily norethisterone acetate is very much lower than most commercially available contraceptive preparations. The failure rate of nine per 100 woman-years resembles the failure rate of mechanical methods of contraception (see Table

6) and also is similar to the failure rate reported for 0·5 mg daily chlormadinone acetate in various British trials (Butler & Hill, 1969; Howard *et al.*, 1969; Leeton, 1969).

The incidence of side-effects in the present study was low, though cycle irregularity was a predominant feature.

An examination of the effects of the preparation on urinary steroid excretion reveals no uniform effects (Figs. 1–5). On the basis of pregnanediol excretion, all subjects were ovulating normally in their pretreatment cycles, but one became certainly anovulatory during treatment (Fig. 4). It is commonly considered that, using the Klopper, Michie & Brown (1959) assay, a pregnanediol peak of more than 2·5 mg/day is essential as a criterion for certain ovulation. Using this criterion two further patients (Figs. 1 and 2) may not have ovulated. Hence, of five certain ovulations pretreatment, there are only two certain ovulations in the first cycle of medication.

Oestrogen excretion in all subjects was little influenced, though there was a tendency for luteal phase oestrogens to be somewhat diminished.

TABLE 6. Effectiveness of various methods of conception control (from Pincus, 1965)

Method	Average pregnancies per 100 woman-years
No contraception	115
Douche	31
Safe period (rhythm)	24
Jelly alone	20
Withdrawal	18
Condom	14
Diaphragm (with or without jelly)	12
Sequential oral contraceptives	1·5
Combined oral contraceptives	<0·1

The data on hormone excretion indicate that ovulation suppression was not the sole, or even the major, contraceptive action of the preparation. The present study was unable to investigate effects on cervical mucous, sperm capacitation, or endometrial histology: all of which may be involved in the mode of action of mini-pills according to other published studies (Maqueo *et al.*, 1963; Gibor, Cohen & Scommega, 1969; Roland, 1968).

Serum transaminases were normal throughout and there was no influence on glucose tolerance or kidney function tests.

Again unlike the combined oral contraceptives, effects on mineral metabolism were small. The combined products induce a mild hypomagnesaemic and hypophosphataemic state (Briggs *et al.*, 1970), but such changes were undetected with this product. The marked increase in copper and ceruloplasmin seen with all oestrogen containing products was absent, but surprisingly, increases in serum iron and iron-binding capacity did occur. This suggests that the latter effects are progestogen rather than oestrogen, controlled.

In general, a daily continuous dose of 0·3 mg norethisterone acetate has much reduced metabolic effects, as compared with other commercially available preparations. It appears

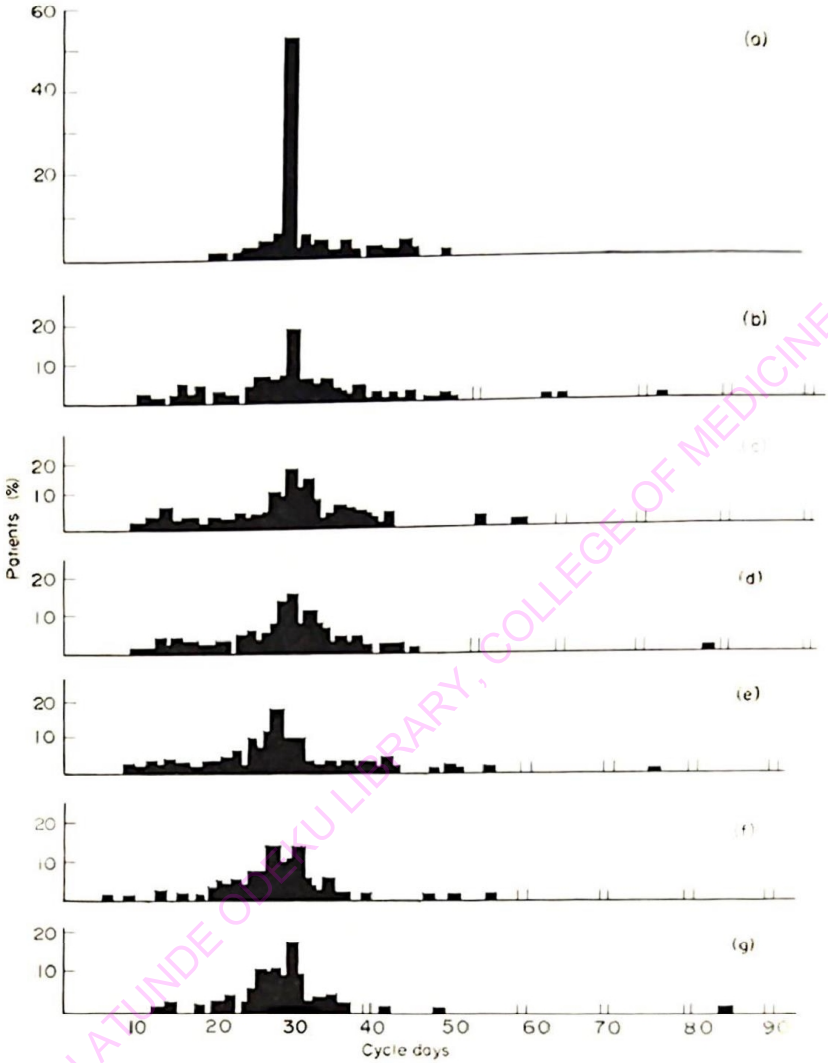

FIG. 6. Effect on cycle length. (a) pretreatment cycle; (b)–(g) treatment cycles 1–6.

to offer a method of contraception free from major side-effects, but with marked cycle irregularity. Its efficacy is about that of physical methods of contraception.

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