

Henderson, the full-time research secretary of the South African M.S. Society, for her unremitting hard work, and also to Mrs. May Munro and Mrs. Phyllis Basford.

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## Daily Progestogen for Contraception: a Clinical Study

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The principal technique of hormonal methods of contraception, based on original studies by Pincus *et al.* (1958), has relied on the joint action of an oestrogen (mestranol) and a progestogen (norethynodrel) given cyclically for 20 days monthly. Combinations of other progestogens with either mestranol or ethinyloestradiol have also been studied. The biological and clinical basis of the antifertility effects of these agents were reviewed by Diczfalussy (1965) and by Rudel and Kincl (1966). The contraceptive mechanisms were described as (1) inhibition of ovulation, by both the oestrogen and the progestogen; and, from the anti-oestrogenic action of the progestogen, (2) a suppressed endometrium unfavourable to nidation, with (3) a cervical mucus hostile to spermatozoal motility. Definitive data on human tubal physiology relating to these agents have not been reported. Mestranol or ethinyloestradiol, given early and with regularity before ovulation, consistently inhibits its occurrence (Rudel and Martinez-Manautou, 1964; Martinez-Manautou and Rudel, 1966). Similar observations were made for ethinyloestradiol by Greenblatt *et al.* (1954). Thus, with the anti-ovulatory role of oestrogen and the anti-oestrogenic effects of progestogen defined, the concept of sequential therapy evolved—that is, early oestrogen for inhibition of ovulation, and later oestrogen plus progestogen to promote maturation of the endometrium with regular withdrawal bleeding. Oestrogen and progestogen, used concomitantly or sequentially, suppress the hypothalamic-pituitary-gonadal cycle, thus preventing ovulation and the normal endogenous regulation of the uterine bleeding cycle.

On evaluating the contraceptive potential of the progestogen chlormadinone acetate in a daily dosage range of 0.5 mg. to 4 mg., a sensitivity differential was found between dosage and

the development and degree of (1) inhibition of cervical mucus fluidity, (2) suppression of the endometrium, and (3) inhibition of ovulation (Rudel, 1964; Rudel *et al.*, 1965, 1967; Martinez-Manautou and Rudel, 1967). Within this range the highest doses produced all three effects, whereas on reducing the dosage to 0.5 mg. only inhibition of the cervical mucus was uniformly maintained; there was some endometrial suppression and, to a lesser degree, inhibition of ovulation. Though, originally, small numbers of women were studied, no pregnancies were seen with chlormadinone acetate 0.5 mg. daily. This suggested a method in which progestogen given uninterruptedly in small daily doses produces contraception without inhibiting ovulation, and if the pituitary-gonadal axis is not interrupted normal menstruation would occur.

Prompted by these observations, Martinez-Manautou *et al.* (1966) carried out a clinical study to define the contraceptive effectiveness of a continuous daily dose of chlormadinone acetate 0.5 mg. Three hundred and twenty women were observed for 1,214 cycles, and two pregnancies were reported—one, as a failure of the method. Approximately 60% of the group had cycles ranging between 24 and 34 days. Because of the simplicity and acceptability, as well as effectiveness, of the method, these studies were extended, and the results are the subject of this paper. Since there is a possibility of lactating mothers becoming pregnant, nursing mothers were admitted to the programme.

### Material and Methods

Chlormadinone acetate 0.5 mg. daily was given continuously to two groups of fertile women. Group 1 comprised 945 non-lactating regularly menstruating women under 36 years of age, and group 2 comprised 100 lactating women, varying from 1 to 15 months post partum. Each received a thorough gynaecological examination, with a Papanicolaou smear, the latter

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repeated at approximately six-monthly intervals. In the menstruating group treatment started on day five of the cycle, and in the lactating group on the day of the first clinic visit. One tablet of chlormadinone acetate (0.5 mg.) was prescribed daily without interruption, regardless of the bleeding pattern. All women were seen monthly and a clinic record was kept of days during the month when bleeding occurred. To detect any possible side-effects, each was carefully questioned and complaints were noted.

To assess the antifertility mechanisms of this method, pertinent studies were done in the non-lactating group on a random basis. These include the following.

**Antifertility Mechanisms (Special Studies)**

1. *Pregnanediol*.—The 24-hour urinary excretion of pregnanediol was determined by the method of Goldzieher and Nakamura (1962). Urine collections were made once during a cycle, and in an endeavour to be within the expected luteal phase—that is, 2–11 days previous to menstruation—the tests were done between days 19 and 21. Values greater than 1.2 mg. per 24 hours indicate ovulation, whereas values of 1 to 1.2 mg. per 24 hours are suggestive.

2. *Endometrial Biopsies*.—In 202 patients these were done once, or more often, usually during the latter part of the cycle. Specimens were fixed in cold (4° C.) buffered formalin, then stained with haematoxylin and eosin. Histological changes were categorized as (1) normal secretory (datable to cycle day), (2) proliferative, and depending upon the suppression of the endometrium as evidenced by the degree of glandular tortuosity and secretion into (3) irregular secretory, (4) irregular, and (5) inactive.

3. *Culdoscopy, Endometrial Biopsy, and Pregnanediol*.—To determine ovarian activity, culdoscopies with photographs were done between days 17 and 23 in 24 selected women, ranging from cycles 1 to 10. Ovarian biopsies were taken in five of these subjects. Twenty of the group had endometrial biopsies, and pregnanediol was estimated in 16 (see Table III).

4. *Cervical Mucus*.—Post-coital sperm count and motility in cervical mucus (Sims–Huhner test) were observed between days 9 and 16 in 115 women. Microscopical examinations were made of the number and motility of spermatozoa in post-coital (one to eight hours, with a mean of five hours) cervical mucus (see Table IV).

**Results**

*Effectiveness Rate*.—Nine hundred and forty-five women on the drug were treated for 8,108 calendar months, representing 8,091 cycles; thus the actual discrepancy between calendar months and menstrual cycles is very narrow. Thirteen of the 14 pregnancies which occurred were attributed to medication omissions—failure to take the pill for several days. The “pregnancy rate”—that is, the pregnancies per 100 women-years of experience (Tietze, 1962)—adjusted for these patient failures is 0.2. However, the “use-effectiveness pregnancy rate,” in which all non-intentional pregnancies, regardless of reasons, are included, may be preferred in assessing the value of a contraceptive method for public-sponsored programmes. Based on these data, the rate is 2.1.

*Menstrual Patterns*.—In distribution, menstrual cycle length in the non-lactating group from cycle to cycle is relatively constant. Between 60% and 74% of women for any given month had a cycle length of 25 to 35 days. The proportions

are in agreement with earlier findings. Individual patients have had one or more randomly occurring cycles of shorter (21) or longer (35) duration. Approximately a third of the patients were completely free of cycle irregularity. Bleeding occurring at intervals of less than 21 days is classified as intermenstrual or breakthrough bleeding (Table I). Though 20.5% had breakthrough bleeding in cycle 1, this decreased to 11.9% by the fifth cycle. Amenorrhoeic cycles of 60 days or longer occurred 169 times, or 2.4% of all cycles.

*Special Studies*.—(1) *Pregnanediol*: Estimations were made for 140 women. Values indicative of ovulation (1 mg. or more) were obtained in 28.5%. (2) *Endometrial Biopsy*: Biopsies were done on 202 women during the last 13 days of the cycle. Results are summarized in Table II. 65.3% were normal secretory or irregular secretory, which we believe to be indicative of ovulation. In those patients with normal secretory endometria the menstrual cycle length ranged from 20 to 36 days in 90%. (3) *Culdoscopy, Endometrial Biopsy, and Pregnanediol*: The correlation of these combined studies is shown in Table III. (4) *Sims–Huhner Test*: Results were negative or poor in 80% of the women studied. None was “excellent” (Table IV).

*Lactating Group*.—Contraceptive treatment in the lactating group was begun between the first and fifteenth month post partum, and extended for a total of 544 months. There were no pregnancies. Menstruation was re-established in 37 women

TABLE II.—Result of Endometrial Biopsy in 202 Cases

Classification of Endometria	No. of Patients	Percentage	
		Category	Accumulative
Secretory .. .. .	61	30.2	
Irregular secretory .. .. .	71	35.1	65.3
Irregular .. .. .	35	17.3	82.6
Proliferative .. .. .	23	11.4	94.0
Inactive .. .. .	12	6.0	100.0

TABLE III

Cycle	No. of Patients	Culdoscopy		Endometrial Biopsy					Pregnanediol	
		Active Follicle	Corpora Lutea	Secretory	Irregular Secretory	Irregular	Proliferative	Inactive	> 1 mg.	< 1 mg.
1	6	1	5	3	1	1	1	0	4	1
2	4	1	3	1	2	0	0	1	3	0
3	5	0	5	4	0	0	0	0	3	0
4	1	0	1	0	0	1	0	0	1	0
5	3	0	3	0	1	0	0	0	1	0
6	1	0	1	2	0	0	0	0	2	0
7	0	0	0	0	0	0	0	0	0	1
8	1	0	1	0	0	0	0	0	0	0
9	1	0	1	0	0	0	0	0	0	0
10	2	0	2	2	0	0	0	0	0	0
Total	24	2	22	12	4	2	1	1	13	3
Percentage		8	92	60	20	10	5	5	81	19

Note.—(1) 24 patients had culdoscopy between days 17 and 23 of the cycle. Of these, 20 had endometrial biopsy between days 17 and 28 of the cycle and 16 had pregnanediol between days 18 and 23 of the cycle. (2) In five patients visual impression by culdoscopy was confirmed by ovarian biopsy.

TABLE IV.—Results of Sims–Huhner Test in 115 Cases

Classification	Spermatozoa		Patients	
	No. per Field (400 ×)	Motility	No.	%
Negative .. .. .	0	—	15	13.0
Poor .. .. .	Scanty	0	77	67.0
Fair .. .. .	1–5	3–4+	17	14.8
Good .. .. .	6–10	3–4+	6	5.2
Excellent .. .. .	> 10	3–4+	0	—

TABLE I

Cycle:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
No. of patients	945	903	860	811	753	668	575	499	408	345	285	238	202	164	131	101	73	52	38	21
Breakthrough bleeding (%)	20.5	20.9	17.2	16.5	11.9	11.3	10.4	10.2	9.0	14.2	8.7	13.0	10.3	7.9	7.6	11.8	5.4	9.6	5.4	0
Amenorrhoea .. .. .	27	18	28	21	14	15	7	8	7	11	4	3	2	1	0	1	0	0	0	0

while on the drug, which indicates that chlormadinone acetate (0.5 mg. daily) may not interfere with post-partum return of the hypothalamic-pituitary-gonadal function (Table V).

**Adverse Reactions.**—Other than bleeding irregularities, the few adverse reactions or complaints, which may or may not be associated with the use of the drug, were generally benign (Table VI). Either voluntarily, or as a result of method or patient failure, there was a pregnancy incidence. Seven women delivered full-term healthy babies. In addition, of seven abortions reported, only one was known to be spontaneous, and was a normal female foetus.

TABLE V

Admissions		Duration of Therapy			First Post-partum Menses	
Post-partum Month	No. of Patients	No. of Patients	Months of Therapy	Women-months	Month of Therapy	No. of Patients
1	11	0	1		1	18
2	24	5	2	10	2	3
3	8	17	3	51	3	5
4	8	23	4	92	4	5
5	7	8	5	40	5	1
6	15	15	6	90	6	2
7	7	13	7	91	7	2
8	6	7	8	56	8	—
9	4	7	9	63	9	1
10	1	4	10	40		
11	4	1	11	11		
13	2					
15	3					
Total	100	100		544		37

TABLE VI

Complaints*	Approximate Incidence
Acne .. .. .	1%
Chloasma .. .. .	2%†
Irritability .. .. .	5%
Pre-menstrual syndrome:	
Abdominal and pelvic cramping .. .. .	3%
Pelvic fullness .. .. .	4%
Mastalgia .. .. .	1%

\* Other than bleeding irregularities. † Increase in pre-existing, or de novo.

**Papanicolaou Tests.**—None of the women developed abnormal cytology (Papanicolaou smears) during the relatively short period of observation.

**Acceptability.**—Acceptance of the method was excellent, and relatively few withdrew from the study. Of 154 (16%) patients discontinuing the programme, only 16 (1.7%) did so because of bleeding irregularities, and 3 (0.3%) for other medical reasons.

### Discussion

Contraceptive action of the progestogen does not depend on the interruption of gonadotrophic and gonadal hormone production, as indicated by the high incidence of normal secretory and irregular secretory endometria (65.3%, Table II). The 24-hour urinary pregnanediol excretions tend to confirm this (Table III). Culdoscopy visualization of the ovary and ovarian biopsies demonstrating corpora lutea also indicate normal gonadal function (Table III). Nevertheless, knowledge is yet too meagre to state without equivocation that disruption of the hypothalamic-pituitary axis is not a factor.

Results of studies of cervical mucus correlate with the observed antifertility effects of chlormadinone acetate, but until prevention of spermatozoal penetration has been demonstrated we cannot be certain that the observed mucus changes are functionally important. Thus the ultimate understanding of all the antifertility mechanisms of this method depends on extended studies to include tubal secretion, egg or blastocyst transport, tubal and uterine motility, as well as definitive observations on gonadotrophins and ovulation and actual demonstration of failure of spermatozoa penetration. Meantime, research indicates that the current low-dose chlormadinone acetate (except for possible dose modifications) is already prac-

tical and, indeed, in certain societies may be eminently acceptable. Chlormadinone acetate is contraceptive to a degree achieved by combination and sequential methods, without inhibiting ovulation.

Goldzieher and Maas (1965) summarized use-effectiveness of several combinations in which the pregnancy rate varies from 0 to 3.1. Furthermore, the same authors, with a sequential regimen of mestranol and chlormadinone acetate, obtained a pregnancy rate of 1.3 in 182,085 treatment cycles. Thus the use-effectiveness pregnancy rate of 2.1 for chlormadinone acetate 0.5 mg. falls well within the rates established for combination and sequential methods. Continuous daily chlormadinone acetate has the obvious advantage of simplicity, which in a public-sponsored programme would be of inestimable value. Menstrual irregularities, which are the chief problem of the method, may be dose-regulated and, hopefully, may be resolved by lowering the dosage (Martinez-Manauto and Rudel, 1967).

If family planning is to succeed in the developing countries it is vitally important to control fertility as soon after delivery as possible. Since breast-feeding is the main source of safe and adequate nutrition in these countries, it is essential that the contraceptive method does not reduce lactation. Once nursing needs are established, hormones, even oestrogen, do not appear to reduce lactation, but since lactation is susceptible to hormonal inhibition in the immediate post-partum period, objective observations are necessary before we can state to what extent, if any, chlormadinone acetate inhibits lactation.

### Summary

Chlormadinone acetate, one tablet (0.5 mg.) daily, was given without interruption to two groups of fertile women, 945 non-lactating and 100 lactating, for contraception, for a total of 8,652 months. Conception was successfully prevented without inhibiting ovulation, and with endogenous hormonal control of cycle bleeding.

Whereas endometrial suppression and inhibition of cervical mucus demonstrated the anti-oestrogenic property of the progestogen, the degree of fertility protection cannot be explained solely on these mechanisms.

Chlormadinone acetate provides contraception during the lactation period and was not found to interfere with nursing needs.

Other than bleeding irregularities, which may be overcome by using still lower dosage, chlormadinone acetate was found to be remarkably benign.

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