The Bulletin of the
Kandang Kerbau Hospital,
Singapore.
Vol. V—No. 1—March, 1966

Sequential formulae and serial regimes of oral contraceptives

(A Report of Singapore Experience of 500 Cycles)

by

T. H. Lean, FRCS, FRACS, FRCOG.

KANDANG KERBAU HOSPITAL, SINGAPORE.

The present state of knowledge and present experiences with oral contraceptives have allowed this method of conception control to reach effectiveness as close to 0·1 to 1·0 per cent (Wiseman). Of the failures using the conventional formulae of the oral contraceptives, attention has been drawn by Mears, Goldzieher and Pincus to what has veen termed as "tablet" and "patient" failures; and Pincus has shown that pregnancies can be expected to occur in cases of omission of tables viz. "patient" failure. Such failures however have not at all proved disastrous as is shown in Table 1. The high failure rate recorded by Peberdy in Newcastle at 9 per 100 Woman Years involved problem families and should not be taken strictly for consideration.

Studies and experiences over the past 10 years using the various available oral contraceptives with the Conventional Formula, however, have recorded objectionable side-effects as close to 23·3—7·7 per cent (G. Pincus). Clearly improvements in the formulae need to be invoked in order to reduce or obviate such side-effects.

It has been apparent that many of the undesirable side-effects are due to the high Progestin dosage in the conventional formulae. Many workers including Binks, McBride and Wiseman have drawn attention to the fact that a reduction of the progestin dosage can bring about a consequent reduction of the untoward side-effects. These side-effects in the main, include:—

Nausea and Vomitting
Headaches and Depression
Decreased Libido
Break-Through Bleeding
Amenorrhoea
Brest Discomfort
Vaginal Discharge
Weight Gain and Weight Loss.

To daythere is no dispute to the concept that Estrogens given alone can inhibit ovulation. Indeed estrogens are now used for ovulation inhbition and the progestins for cycle control. This concept is not at all new for as early as 1937, Kuzrok had used estrogens in the treatment of dysmenorrhoea to inhibit ovulation. Lyon in 1943, using basal body temperature charts, showed that 0·05 mg. of ethinyl estradiol given for 20 days from the 4th or 5th day of the cycle can inhibit ovulation. The exact dosage of estrogen for ovulation inhibition has however not been established with any specific clarity. Lyon showed that 50 γ (0·05 mg) of ethinyl estradiol for 20 days from day 5 of the cycle can inhibit ovulation but McBride pointed to the presence of ovulation escape with dosage of 80 γ (0·08 mg) or less. Martinez-Manitou et al found 80 γ of mestranol as a satisfactory level to inhibit ovulation. Impressions today in the majority define 100 γ (0·1 mg) of mestranol or ethinyl estradiol as a safe and effective level to supress Follicle Stimulating Hormone activity and follicular development. Estrogens will cause nausea and vomitting when administered orally in some patients but this reaction tend to decrease as tolerance develops in the individual. Newer estrogens can be evolved which can reduce further the incidence of this side-effect.

TABLE I

Failure Rates with Oral Contraceptives

Investigator	Country	Women	Cycles	Pregnancy Per 100 Woman Years
Goldzieher	U.S.A. (Orthonovum 10 mg.)	210	12147	0
Mears	U.K.	1913	20000	0.74
Peberdo	U.K. (Newcastle Problem Families)	70	1186	9
Pincus	Puerto Rico and Haiti	1500	25429	1·7
Rice Wray	Mexico	5379	37463	0.52
McBride	Australia (Serial)	450	3462	0

Based on the above impressions, various formulae of a progestin/estrogen combination have been evolved in the various oral contraceptives with the conventional formulae. The ideal is to invoke a formula using estrogens as the ovulation inhibitor—preferably estrogens causing little or no side-effects and progestins for cycle-control—and preferably low dosage progestins so that side-effects can also be minimised or obviated. The multiple methodology for the oral contraceptives today represents a continued search for an ideal formula. The concept of a sequential formula for incorporation as an oral contraceptive had been suggested by Fuller Albright as early as 1945, and Greenblatt had developed this sequential regime in the management for dysmenorrhoea—using ethisterone to induce withdrawal bleeding. Greenblatt developed this sequential formula in 1959 using ethinyl estradiol followed by dimethisterone. The term "sequential" had actually been coined by Goldzieher in 1963 and the original formulation as used by him and his co-workers consisted of 15 days of mestranol (not less than 80 γ) followed by a further 5 days of the same mestranol to which 2 mgms of chlormadinone has been added. A further development to this sequential regime is an extension of 7 days of placebo tablets making the term Serial regimen in vogue. The Serial regimen thus consists of a pill a day for 28 days and taken continuously.—See Tables II and III.

TABLE II

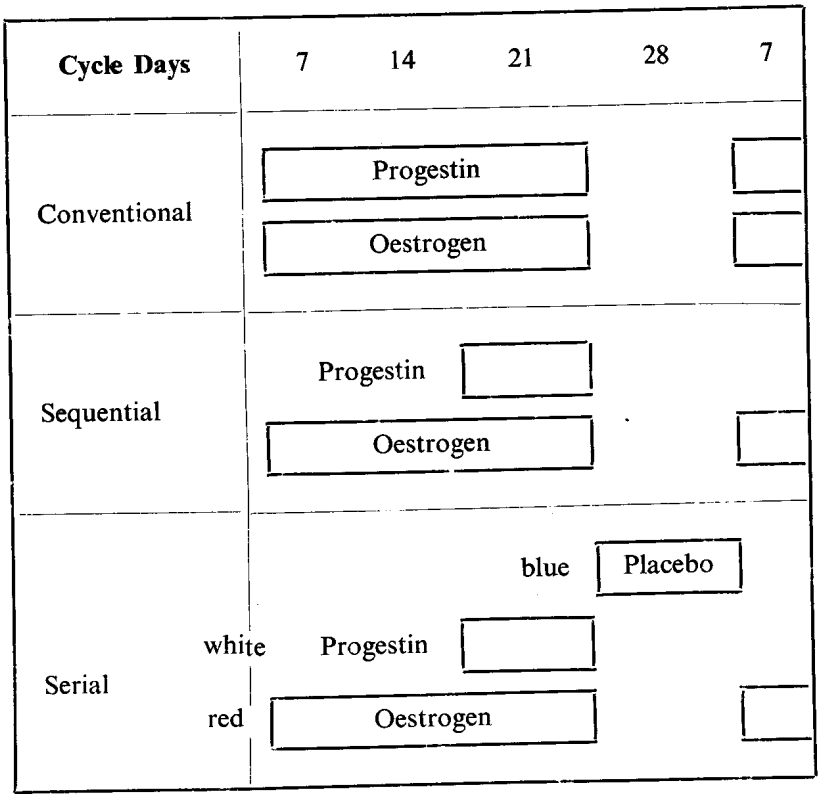

TABLE III

The present report is based on a preliminary study of 500 cycles using a serial formulation as follows:—

Ethinyl Estradiol 0.075 mgm for the first 16 days.

followed by

Ethinyl Estradiol 0·05 mg with) } for the next 5 days
Megoestrol Acetate 4 mg)

and followed by

Placebo of Lactose Tables for the following 7 days.

Types of Patients

A total of 44 women patients within the age-groups 25 to 35 yars of age were selected for inclusion in this study. They were well-educated women and whose family were within what may be termed as a "Upper Middle Class" in Singapore. The combined earning capacity of the family averaged about $1000/— Singapore Dollars per mensem. The selection of patients was deemed necessary so as to obviate "Patients Failure" and also to make easy and complete the varous data which were being sought in the study. Thirty-six (36) patients belonged to the Chinese race and eight (8) were Tamils (Southern Indians).

Pregnancy Rate

There had been one (1) case of failure resulting in a pregnancy in an Indian patient —age 35 years—parity six. This pregnancy had since been carried to term and delivered. A female infant without any developmental abnormality and in good condition was delivered. The patient had been sterilised by Salpingectomy after the delivery and had not been too disappointed over the "Pill Failure" for she had six children who are all male and this pregnancy was the female child she and her husband had waited for a long time.

TABLE IV

Data on Pregnancy Rates with Different Serial Formulations

(Auckland Experiences (Liggins), Singapore Experiences & Sydney Experiences (McBride))

Formulation			No. of		Total
16 Days	5 Days	7 Days	Women	Cycles	Pregnancies
Liggins (Auckland)					
EE 0·075 mg	EE 0·05 M.A. 4 mg	Inert	509	3000	32 : Rate 12·8
EE 0·075 mg	EE 0·075 M.A. 4 mg	Inert	100	2471	13 : Rate 6·3
EE 0·1	EE 0·1 M.A. 1 mg	Inert	520	3824	1 Failed to take
EF 0·1	EE 0·1 M.A. 5 mg	Inert	177	866	None
McBride (Sydney)					
EE 0·1	EE 0·1 m.A. 5 mg	Inert	450	3462	None
Singapore					
EE 0·075	EE 0·05 M.A. 4 mg	Inert	44	500	1 : Rate 2·4

This single failure represented a pregnancy rate of 2·4 per 100 woman years and compared with other studies using various formulations of both the sequential and serial regimes, the figures were as follows:—

The above figures confirm the observation that oral contraceptives employing estrogens at a dose less than 80 γ (0·08 mg) will allow ovulation escape. The safer dose is to ensure that the dose is not less than 100 γ (0·1 mg) of ethinyl estradiol. (EE)

Side Effects

As expressed in the introductory paragraphs, the desirability of an ideal contraceptive pill is not only to achieve complete success but also to give rise to little or no objectionable side-effects

The comparative data on the various side-effects reported on the use of the sequential serial regmes are shown in Table V and VI.

On the whole, it can be accepted that except for the McBride studies, the incidence of objectionable side-effects using the various sequential formulae are desirably low. The reduction of progestins considerably reduced the weight gain and mastalgia. Nausea and vomitting appear to be estrogen induced rather than a side effects or progestin therapy. The Singapore studies with a lower dose estrogen formula had the lowest incidence of nausea and vomitting. Clearly there is a problem with this variation. Low dosage estrogen—if less than 0·8 mg might allow ovulation escape and higher dosages will tend to increase the incidence of nausea and vomitting. Perhaps newer

TABLE V

Investigation	No. of Patients	Cycles	Nausea 1st Cycle	Nausea Overall	B.T.B. 1st Cycle	B.T.B. Overall	Amenorr-hoea
McBride (Australia)	450	3462	14	2·3	-	2·6	0·9%
Courtenay (West Indies)	72	466	-	1·3	-	0·9	-
Chinnatamby (Ceylon)	141	552	12	4·0	0·7	0·8	-
F.P.A. (London)	22	230	10	2·0	-	0·5	0·5
Singapore	44	500	3	0·2	-	-	-

Data on Formulations:

	Ethinyl Estradiol	Megestrol Acetate
Australia	0·1 mg	1 mg
West Indies	0·1 mg	1 mg
Ceylon	0·1 mg	5 mg
London	0·1 mg	5 mg
Singapore	0·075 mg	4 mg

TABLE VI

(Overall Incidence) Per Cent

Side-Effects	Australia	West Indies	Ceylon	London	Singapore
Nausea	2·3	1·3	4·0	2	0·2
Breast Discomfort	0	0·5	0	2	0
Vaginal Discharge	17	0	0	0	0
Break-Through Bleeding	2.6	0·9	0·8	0·5	0
Amenorrhoea	0·9	0	0	0·5	0
Oligomenorrhoea	2·6	0	0	0	0
enorrhagia	0·6	0	0	0	0
Weight Gain	4·0	0·5	0	0·75	1·5
Weight Loss	33·1	0·5	0	3·9	0·5

estrogens will be available soon so that an optimal compound with an optimal dose can be employed which can achieve 100 per cent ovulation inhibition and zero incidence of side-effects of nausea and vomitting. The Australian study hsowed a high incidence of vaginal discharge but McBride has pointed out that there had been a high incidence of cervicitis amongst his patients and he advises that cervicitis must be treated first before commencement of the oral contraceptives. The vaginal discharge is due to action of estrogens on the cervical glands. The high incidence of weight loss amongst patients in the Australian series at 33·1 per cent will appear to be a dissension factor. This observation was not obtained with the other studies including the Singapore study and an explanation is still forthcoming on this issue. McBride however did point out that the reaction rate amongst those patients using oral contraceptives for the first time (82 out of 450 patients) was noticeably better than those amongst the transfer patients who had been on some other contraceptive pills. The Singapore study involved all patients who are new to oral contraceptive therapy.

Clearly the use of the sequential/serial methodology of oral contraceptive pills marks a great step forward in Ovulation control. The rate of effectivity is very high provided the estrogen dose does not fall below 80 γ of ethinyl estradiol. The relative increase in the freedom from reactions and its apparent ease of administration—a pill a day—enhances its aesthetic value and should obtain a high rate of acceptability amongst women in the world.

Summary

1. The evolution of a sequential and serial regime as a method of oral contraception is described. There appears to be general agreement that estrogens in a dose not less than 0·8 mg of ethinyl estradiol (80 γ) given in the first 16 days of the cycle can effectively inhibit ovulation; and progestins given for 5 days from the 17th to the 21st day of the cycle can be relied on to produce cycle control of the endometrium.
2. Comparative results of a Singapore experience of 500 cycles using a sequential formula of Ethinyl Estradiol 0·075 mg given for the first 16 days and followed by Ethinyl Estradiol 0·05 mg and Megestrol Acetate 4 mg for the next 5 days with a subsequent 7 days of placebo—making a regime of 28 pills—are compared with other sequential and serial regimes in other countries. A pregnancy rate of 2·4 per 100 woman years was obtained in the Singapore study but minimal sideeffects were recorded in the survey.
3. There appears to be evidence to show that the sequential formula will obtain a higher rate of acceptability—very much so if a newer estrogen with an effective ovulation inhibition dose and absent side-effects is evolved.

Acknowlegment

The supply of the oral contraceptives in this Singapore experience had been supplied by British Drug Houses Ltd. to whom the author is grateful.

References

Albright, Fuller, (1945): "*Internal Medicine, Its Theory and Practice*", p.966, Philadelphia; Lee J. Febeger.

Cox, H.J.E., (1965): I, Bull. Kandang Kerbau Hospital, Singapore, 4, (2) 90-106 2. Personal Communication.

Garcia, C.R., (1964): Clin. Obstet. Gynaec. 7, 844.

Goldzieher, J.W., (1964): Med. Clins. N. Amer., 48, 2.

Goldzieher, J.W., (1964): Am. J. Obstet Gynaec. 90, 404.

Goldzieher, J.W., (1963): West. J. Surg. Obstf Gynaec. 71, 187.

Goldzieher, J.W., (1964): Proc. Seventh Conf. I.P.P.F., Singapore et al.

Greenblatt, R.B., (1958): Am. J. Obstet. Gynaec. 76, 626.

Greenblatt, R.B., (1962): obstet. Gynaec. 19, 730.

Greenblatt, R.B., (1954): Am. J. Obstet. Gynaec. 68, 835.

Kurzrok, R., J. (1939): Contracept. 2, 27-29.

Liggins, G.C., New Zealand Conference, Obstetrics & Gynaecology, Hammer Spring, New Zealand, February, 1964.

Liggins, G.C., (1964): Paper read at University College Hospital, London.

Liggins, G.C., Recent Advances in Ovarian and Synthetic Steroids. Proceedings of Symposium, Sydney, October 1964.

Lyon, R.A., (1943): Surgery Gynaec. Obstet. 77, 657.

Martinez-Manauton, J., Eleventh Reunion Nacional de Ginecologiay Obstetricia, Guadalgora, Mexico, July 10, 1962.

McBride, W., Recent Advances in Ovarian and Synthetic Steroids. Proceedings of Symposium, Sydney, October 1964.

McBride, W., Letter—Med. J. Australia, Apr. 3, 1965, 525.

McBride, W.G., (1965): Med. J. Aust. 1, 525.

Pincus, G., (1957): Acta Endocr. Copenh. 23, Supp. 28, 18-36.

Pincus, G., (1958): Am. J. Obstet. Gynaec. 75, 1333.

Pincus, G., (1959): 6th International Conference on Planned Parenthood, Delhi, Feb. 14-21.

Pincus, G., (1961): "*Modern Trends in Endocrinology*", H. Gardiner Hill ; London, Butterworth.

Pincus, G., (1965): "*The Control of Fertility*": Academic Press.

Pincus, G., (1961): Bull. of Postgraduate Committee in Medicine, Sydney, pp. 127-136

Puddy, E.M., Recent Advances in Ovarian and Synthetic Steroids. Proceedings of Symposium, Sydney, October 1964.

Wiseman, A., Third International Seminar on Seminar on Obstetrics and Gynaecology, Ankara, Turkey, October 1963.

Wiseman, A., Recent Advances in Ovarian and Synthetic Steroids. Proceedings of Symposium, Sydney, 1964.