A CLINICAL STUDY OF AN ORAL CONTRACEPTIVE IN SINGAPORE

By S. C. Hu, M.B., D.P.H.

and

S. M. Yung, M.B.B.S.

(Maternal and Child Health Services, Singapore)

In July, 1963, a clinical trial of a new low dosage oral contraceptive was started in two Maternal and Child Health Clinics at Queenstown and Bukit Ho Swee. The objects were to assess the acceptability of contraceptive pills in Singapore women and to test the efficacy of this new product which was to be released commercially a year later as "Ovulen". The tablet consists of ethynodial diacetate 1 mgm. (labelled then as SC11800) with Mestranol 0·1 mgm.

At the end of August 1965, 26 months after the first consultation, 204 women have been studied over periods ranging from 1 to 29 cycles totalling 2363 cycles. 57 women have withdrawn because of various reasons.

THE PATIENTS

The participants were selected from postnatal mothers or mothers accompanying their pre-school children to these clinics. Their ages were between 17 and 41 years, and they were of proven fertility having an average number of 5·7 pregnacies. One of them had 16 pregnancies with 14 living children. Most of them were from the lower income group. The majority were illiterate, but were keen on this method of contraception, and sufficiently intelligent to count dates and remember instructions. 27 per cent have never used any form of contraceptive previously. Four races were represented:

Chinese	Malay	Indian	Eurasian
169	21	13	1

METHOD

At the first visit, the medical, obstetrical, gynaecological and marital histories were recorded. The body weight was taken. This was followed by a physical and pelvic examination. Laboratory tests included blood for haemoglobin and urine for albuminuria and glycosuria. With the exception of mild cervical erosions, women with clinical pelvic abnormalities and the presence of cardiac, liver, renal diseases, thyrotoxicosis, diabetes and thrombophlebitis were excluded from the trial.

Each new patient was supplied with a vial of 20 pills one to be taken every night from Day 5 of the menses until all were taken. They were to return when withdrawal bleeding or breakthrough bleeding occurred or if there was no withdrawal bleeding 5 days after the 20th pill. On day 5 of the next cycle she was to commence her second course of tablets and so on. In addition many of them were given printed instructions either in Malay or Chinese. The transient nature of the reactions was explained. If the patient had bleeding during medication she was to stop the therapy and to recommence on Day 5 of the bleeding. When she failed to have withdrawal bleeding she was advised to restart the next course after a gap of 5 days. They were also warned that the tablets could not be relied upon for the first 7 days of the first cycle. (Pullen, 1962)

The mothers were interviewed by the doctor or a trained health nurse every month for the first 6 months. Thereafter they were given one to three months supplies and a small note book to record their menstrual history and side effects. If necessary, instructions were repeated and reassurance given during such revisits. When a woman was over due for new supplies, a reminder was posted to her. If she failed to turn up, a health nurse would pay a home visit to interview the woman concerned.

Through the generosity of Searle and Company Limited, 1849 courses were given free to our patients for a period of 6 to 12 months. After these they were given prescriptions for further supplies.

PATIENTS LEAVING TRIAL

The patients who dropped out and their reasons for doing so are illustrated in Table I. Only 12 women (5·9%) withdrew on account of reactions and 6 women (2·9%) because of breakthrough bleeding. The small number of with-

TABLE I

ANALYSIS OF WITHDRAWALS

Reasons for withdrawal	Number of Patients	Number of Cycles Completed
Repeated "breakthrough" bleeding	5	1, 4 (2 women), 5, 7
Poor cycle control with fibroids	1	21
Dizziness and vomiting	3	1 (2 women), 2
Dizziness	3	1 (2 women), 3
Nausea	1	4
Headaches	1	21
Menorrhagia	1	7
Breathlessness	1	1
Skin rashes	1	6
Itching of face	1	1
Husband away	8	1, (3 women), 3, 7, 9, 17, 22
Husband or wife ill	7	1, 2, 3, 6 (2 women), 9, 20
Removed or unable to contact	9	1, 3, 10 (2 women), 13, 15, 16, 17, 19
Not free to come for supplies	4	1 (2 women), 3, 5
Insist of taking pills irregularly	2	5 (advised to stop) 5 (pregnant in 5th cycle)
Preferred IUD	2	10, 15
Already pregnant	1	1
Husband objects	1	6
Husband died	1	9
Planned pregnancy	3	7, 10 (2 women)
No reason given	1	12

TABLE II

ANALYSIS OF REACTIONS

Cycle	1	2	3	4	5	6	7	8	9	10+	Total
No. of Cycles	204	189	186	183	180	174	170	164	154	759	2,363
Nausea	31	4	4	2	1						42
Dizziness	45	18	7	7	1	2		2		1	83
Vomiting	8	1									9
Headache		2	1							3	6
Premenstrual Tension	1										1
Breathlessness	1										1
Palpitations	1	1									2
Rashes			1	1	1	2					5
Tiredness	1	1	1								3
Epigastric Discomfort	3						1				4
Breast Discomfort	5	3	3	1	2	2		1			17
Leucorrhoea	1	1		1		1					4
Itching of face	1										1

TABLE III

PERCENTAGE OF COMMON REACTIONS

Cycle	1	2	3	4	5	6	7	8	9+	All Cycles
Dizziness	22·1%	9·5%	3·7%	3·8%	0·6%	1·1%		1·2%		3·5%
Nausea	14·3%	2·2%	2·2%	1·1%	0·6%					1·8%
Breast Dis-comfort	2·5%	1·6%	1·6%	0·5%	1·1%	1·2%		0·6%	0·1%	0·7%
Vomiting	4·1%	0·5%								0·4%

drawals is evidence that the pill is highly acceptable to the women in this country.

REACTIONS (Tables II and III)

Dizziness and nausea were the 2 most common side-effects. All of these complaints however, were mild. They occurred mainly in the first 2 cycles and were well tolerated by most women. Only 7 women (3·4%) experienced them severe enough to withdraw from the trial.

Headache was not significant. One patient dropped out after having had the pills for 20 woman months because she had headaches before her periods for three consecutive cycles.

One mother who had always had premenstrual breast enlargement, complained of painful engorged breasts with secretion of milk during her 18th cycle. Incidently she gained 4 pounds weight in that month.

Libido was too difficult to assess. Only 2 voluntarily admitted an increase in libido. The rest were probably too embarrassed to admit any difference.

87 cases gained 3 to 18 pounds weight during the trial. 46 women lost from 3 to 14 pounds during the period of study. 71 patients have been having fairly constant weight throughout.

EFFECTS ON THE MENSTRUAL CYCLE (Table IV)

Breakthrough Bleeding and Spotting

Among those 65 cycles where one or two pills have been missed, the cycle control was poor:

B.T.B. - - 30%
Spotting - - 3%

The cycle control was much better when pills had been taken regularly:

B.T.B. - - 2·3% (all cycles)
Spotting - - 1·1% (all cycles)

Evidence showed that intermenstrual bleeding improved with continuance of the medication.

There were 7 women who had repeated breakthrough bleeding despite regular intake of pills. Two were corrected by increasing the dosage to 1½ tablets daily. The rest abandoned the trial.

Amenorrhoea which was a main cause of anxiety was not common. It occurred in 0·8% of all cycles and was mainly found in the first 7 cycles.

The *Menstrual flow* was increased in 9 women while 87 women noticed a marked decrease. Many of these women were quite alarmed at the scanty menstruation because they believed that accumulated menstrual blood in their system would make them ill. Some were afraid that scanty periods were a sign of pregnancy. However, with reassurrance they continued quite happily with the trial. 108 mothers stated there was no change of flow.

Leucorrhoea: One participant complained of excessive mucous vaginal discharge during the medication. On examination her cervix was found to be congested and soft. There was no cervical erosion.

Bearing in mind the differences in racial characteristics, method of questioning and degree of patients' confidence in the staff, the results of this series may be compared with trials using other low dosage oral contraceptives.

TABLE IV

ANALYSIS OF CYCLE CONTROL

Cycle		1	2	3	4	5	6	7	8	9	10+	Total
No. of Cycle		204	189	186	183	180	174	170	164	154	759	2.363
Missed Tablet	B.T.B.	1	3	5		5	1	2		1	4	22
	Spotting	1		1								2
	None	6	5	2	3	4	7	1	2		11	41
Escaped	B.T.B.	7	10	6	9	9		1	4	3	6	55
	Spotting	9	2	3	1		1		1		10	27
Amenorrhoea		1	2	4	5	1	1	2			4	20

"Escaped" means loss of cycle control despite regular intake of pills.

Rice-Wray et al (1962) reported chloasma, hot flushes, headache and nausea as the commonest reaction among 364 Mexican women who were mostly from the lower income group. The product used was "Orthonovum". Only 2·7% of the women rejected the method because of unpleasant side effects. No one withdrew because of bleeding.

No spontaneous complaints regarding nausea, vomiting or gastro-intestinal symtoms were noted by Goldzeiher et al (1962) in 210 women (Mexican 84%, Negros 6%, Caucasian 10%) who were also mainly illiterate and from the lower income group. There was no rejection due to side-effects. No one discontinued because of breakthrough bleeding.

According to a report of the Hong Kong Family Planning Association in 1964, 234 women on Previson had a drop-out rate of 10·3% due to nausea, dizziness and breakthrough bleeding. Nausea and dizziness were the commonest reactions:

Nausea	- -	12% (1st cycle)
Dizziness	- -	7% (1st cycle)

The incidence of bleeding during medication was 7·3% in the 1st cycle.

Bockner (1963) reported headache and nausea as the most significant side-effects among 106 Australian women on "Anovlar", but there were no withdrawals on account of these reactions. On the contrary, 5 women withdrew because of breakthrough bleeding (4·7%). Breakthrough bleeding together with spotting in his series occurred in 32% of the first cycles.

In Slough District, England, 200 patients were given Conovid-E. (Pullen, 1962). Out of these 46% had nausea in the 1st cycle. There were 4 rejections. Although the incidence of breakthrough bleeding in the first cycle was 31%, none abandoned the trial because they accepted a higher dosage of therapy which stopped the frequent bleeding.

FOLLOW-UP

Unplanned Pregnancies

There were 2 unplanned pregnancies. One had already conceived before she started the cyclical therapy. Gestation was not detected because she had 2 normal periods during early pregnancy. A pelvic examination was performed on the 5th week of gestation but she was advised to start the medication only on Day 5 of the following menses. While taking her first course of pills she returned to the "Kampong" for two months. By the time the health nurse got in touch with her the uterus was found to be enlarged to a size consistent with a 16 week pregnancy. This date was confirmed when she delivered a normal male infant five months later.

The second woman did not complete her 5th course of therapy and conceived in the same month. She had a premature infant weighing 3 lbs. 1 oz. and it was clinically normal.

Planned Pregnancies

3 patients withdrew from the trial to have more children. All of them became pregnant within 4 months after discontinuation. One had already given birth to a normal healthy infant. The other 2 are still undelivered.

Vaginal Examination

Pelvic examinations were done at 6 monthly intervals in the first year and every 12 months after that.

Suspicious looking erosions found in 2 patients at the end of 6 months' therapy were referred to the Gynaecological Clinic at Kandang Kerbau Hospital. Papinicolaou smears and biopsies were reported to be non-malignant.

In one woman a small ovarion cyst was detected after 12 months' medication. This was not detected during her 1st visit. It turned out to be a dermoid cyst when it was removed 4 months later.

A mother of 5 children with a bulky uterus before the trial was found to have an enlarged womb after 10 months' therapy. It's size was equivalent to a uterus of 8 week's gestation. Pregnancy was excluded by the gynaecologist and a diagnosis of fibroid uteri was made. Since the fibroid was small, symtomless and she was particularly anxious not to have further childbearing, "Ovulen" therapy was continued. Unfortunately there was a breakdown in the cycle control from the 17th cycle onwards. She had repeated breakthrough bleeding alternating with prolonged periods. The dosage was then increased to 1½ tablets daily but there was no improvement. In addition she complained of severe dysmenorrhoea and menorrhagia. By that time she was unwilling to carry on with the trial and dropped out after 21 cycles.

Thrombophlebitis, Occular Thrombosis and baldness have not been reported.

COMPARISON OF REACTIONS BETWEEN ORAL AND MECHANICAL CONTRACEPTIVES

Since nausea, dizziness, headaches are subjective symptoms, it was thought interesting to compare them with those of mechanical methods

such as vaginal contraceptives and sheaths. The team from the Singapore Family Planning Association who visited Queenstown Maternal and Child Health Clinic once every week was approached to supply the necessary data. They were asked to select 204 new patients on traditional methods and to ask each of them on their return for fresh supplies a set of questions:

1. How have you been?
2. Are your periods regular while on contraceptives?
3. Any dizziness, vomiting and nausea, headache or other complaints?

Out of the 204 patients, only 3 complained of dizziness.

COMMENTS

The problem of training those lacking in education was largely overcome by close supervision and painstaking instructions by the clinic staff and doctor. This was achieved by various ways:

1. Repeated instructions during their monthly interview,
2. Warning beforehand of the transient nature of reactions in order to establish their confidence in the "pill",
3. Keeping records of their menstrual cycles in little note books with the help of their husbands if necessary,
4. Sending reminders to defaulters promptly,
5. Home-visiting.

It was felt that if the women had more confidence in the staff and method and not listen to what their neighbours said, there would be less withdrawals due to side effects.

On the whole the pill has brought great happiness to many women particularly the Malays who have so far been reluctant to accept the conventional methods. Minor discomforts such as dizziness and nausea are far outweighed by the advantages of the medication such as a sense of well being and the absence of anxiety due to unwanted pregnancy. Weight gain which occurred in 43% of women is looked upon as a welcome change especially by the worn out undernourished grandmultiparous mothers.

SUMMARY

1. Two Maternal and Child Health Clinics conducted a clinical trial on "Ovulen" from 26th July 1963 to August 31st 1965. A report is given here on its use involving 204 patients over a period of 26 months. Altogether 2,363 cycles have been studied. The greatest number of cycles reached by one woman was 29.
2. The "pill" is highly acceptable to Singapore women. It is safe and 100 per cent effective during these 2 years. The cycle control is excellent.

	1st. cycle	All cycles
Breakthrough bleeding	3·9%	3·3%
Spotting	4·9%	1·2%
Amenorrhoea	0·5%	0·8%

Reactions are mild and are found mainly in the first cycle.

	1st. cycle	All cycles
Nausea	14·3%	1·8%
Dizziness	22·1%	3·5%

3. No incidence of thrombophlebitis, occular thrombosis or baldness was reported.
4. A comparative study on the reactions between mechanical contraceptives and "Ovulen" is presented. Side effects of conventional methods are negligible.

ACKNOWLEDGEMENTS

We would like to thank Dr. Maggie Lim, Senior Health Officer in charge of the Singapore Maternal and Child Health Services for her encouragement and criticisms of this study and report. We are also grateful to Dr. H. J. E. Cox of Searle and Company Limited for his help in conducting the trial. Co-operation from the staff of both the Maternal and Child Health Clinics in Queenstown and Bukit Ho Swee as well as the Singapore Family Planning Association team at Queenstown is greatly appreciated.

REFERENCES

1. Bockner, V., (1963): "The Contraceptive Pill: A Clinical Evaluation of its Long-term Use", Med. J. Aust., 1,809.
2. Goldzieher, J.W., Moses, L.E. Ellis, L.T. (1962): "The Study of Northindrone in Contraception", J.A.M.A., 180, 359.
3. Hong Kong Family Planning Association (1964): Report on "Previson" Oral Contraceptive Pills.
4. Rice-Wray, E., Schulz-Contreras, M., Guerrero, I., (1962): "Long-term Administration of Norethindrone in Fertility Control", J.A.M.A., 180, 355.
5. Pullen, D., (1962): "Conovid-E" as an Oral Contraceptive, Brit. Med. J., 1,1016.