PILL-A-MONTH AS AN ORAL CONTRACEPTIVE

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Intensive efforts have been made in the last ten years to improve oral contraceptives and to simplify the schedule of their administration. The already available types need to be taken daily for 20 to 30 days each month. This means that the woman should be sufficiently motivated to follow this daily schedule beside her worries of getting pregnant or of having bleeding if she misses a pill or two.

The one pill a month was introduced by Greenblatt (1967) in an attempt to simplify the schedule of oral contraception and as a trial to increase the acceptability of this form of fertility control. We felt it would be interesting to evaluate this simple method in our developing Country where the drop out rate from the conventional type of pills was 65% in the national family planning program during the last five years. The «pill-a-month» combines a long acting oestrogen «Quinestrol and a short acting progestogen «Quingestand». The uniqueness of the combination is primarily dependent on the prolonged activity of the oestrogen component «Quinestrol» ; (17 alpha ethinyl estradiol-3-cyclopentyl ether) 2 mg. Quinestrol is stored in body tissues and subsequently released slowly thus producing a prolonged anti fertility effect.

Quinestrol with H^3 in the steriod nucleus and with C^{14} in the Cyclopentyl group has been studied in women by Williams et al 1967.

Radioactivity was demonstrated in urine over a period of up to 127 days.

(*) We would like to express our appreciation to Professor Dr. Fatma Abdeen for her interpretation of the endometrium, and to Dr. T. Abdel Aziz for his help in the review of the chemical analysis of the pill.

Quinestral was also recovered from body fat after 2 and 3 days following ingestion.

Quingestanol acetate (3 Cyclopentyl ether derivative of norethindrone acetate») is the progestogen component of the pill which induce withdrawal bleeding and regulate the cycle. (Shafetz et al, 1969 and Guilloff et al, 1970).

MATERIAL AND METHOD

This evaluation was undertaken on 1200 cases chosen at random from those attending the Family Planning Clinic at «AL-AZHAR» University Hospital, Cairo. The results of the first 600 cases are presented in this communication. The age of the participants varied between 20-42 years with an average of 31 and their parity varied from 1 to 9. All participants did not use steroid contraceptives for at least 3 months preceeding the trial. A thorough history was taken from cases including an obstetric and a menstrual history.

None of the cases had a past history of jaundice or thrombosis.

All participants were examined at the start of the study. This included breast examination together with recording of the blood pressure and weight. The lower limbs were examined for varicosities. Abdominal and pelvic examination were also performed to exclude any abnormality and a cervical amear was obtained from each case during the first pelvic examination.

REGIMENS OF ADMINISTRATION

Participants were divided into two groups :

Group A, (96 cases). In this group the first pill was given on the 25th day of the cycle to get a withdrawal bleeding at the supposed date of the next flow. Subsequent pills were given monthly on the same day of each calendar month irrespective of the time of onset of menstruation.

Group B (504 cases). In this group the first pill was given on the first day of the menstrual flow and the second pill was given after 3 weeks. Subsequent pills were then given monthly on the same day of each calendar month.

Because of the long acting nature of the oestrogen of the pill, it is not fully effective during the first cycle. To avoid the occurence of pregnancy during that cycle, I.U.D.'s were inserted in cases of Group A and vaginal tablets of phenylmercuric acetate were used by cases of Group B during the first cycle. Cases were instructed to take the pill at bed time after a fatty meal as it has been reported by Giannina (1967) that Quinestrol was absorbed mainly with the fat through the lymphatic system.

FOLLOW UP

Participants were followed up monthly for 6 to 12 months.

The total follow up cycles were 3858.

They received a card indicating the date at which they should take their pill. All cases were asked to report any unusual symptoms.

During each monthly follow up visit, information was obtained about the menstrual pattern and any side effect that followed the intake of the pill. Physical examination was repeated this included examination of the breasts, pelvis, blood pressure estimation and weight recording.

Cervical smears were taken to detect any cellular atypia. Premenstrual endometrial biopsies were taken before the medication in 65 cases and were repeated after 1, 3, 6 and 12 months. Ovarian wedge biopsy was taken from 3 post cessation patients.

TABLE 1

General Aspects of Participants

1. Number of cases	600
2. Number of cycles	3858
3. Number of women who completed 1 year	120
4. Number of previous pregnancies	3851
5. Average number of previous pregnancies per case	6.418
6. Total number of living children	2746
7. Average number of living children per case	4.576
8. Total number of previous abortions	492
9. Average number of previous abortions per case	0.82
10. Number of Lactating cases	106

RESULTS AND COMMENTS

I.—MENSTRUAL PATTERN

1. *The Pill Menstruation Interval* (P. M. I.)

The mean interval in the total cycles was 11.6 days. The flow began 6-15 days after taking the pill in 80.4% of Cycles (Table 2 & 3 and Fig. 1 & 2). A low degree of negative correlation was found between the P. M. I. and the weight of the participants. This can be explained by the finding of Giannina et al 1967 who reported that in rats approximately 20-25% of the administered dose of Quinestrolis stored in body fat. This means that in fatty women, the amount which is stored is much higher than in slimmer women. The effective level of non stored oestrogen being higher in the slim cases can probably lead to a delay in the shedding effect induced by the progestogen component of the pill.

TABLE 2

The Pill Menstruation Interval

Cycle	No. of Cases	Longest Duration	Shortest Duration	Mean
Ia	71	20	1	7.8
II	447	20	1	10.2
III	393	22	2	12.8
IV	374	24	2	13.1
V	367	25	1	12.2
VI	366	22	1	11.2
VII	365	23	1	10.8
VIII	361	20	2	10.7
IX	243	25	3	10.04
X	120	25	2	10.2
XI	120	25	2	11.1
XII	120	25	3	10.1
Total	3858	36	1.75	11.6

TABLE 3

Distribution of the Pill Menstruation Interval

Cycle	Interval (Days)								Total No.
	1—3	4—5	6—7	8—9	10—11	12—13	14—15	16—17	
	Number of Cases								
Ia	13	13	11	10	8	8	3	4	71
II	37	37	60	34	96	38	54	45	401
III	16	28	45	33	116	33	40	60	371
IV	14	23	35	45	120	35	40	45	353
V	11	18	41	44	117	27	35	50	350
VI	9	21	34	47	135	32	43	36	357
VII	10	21	40	60	130	30	34	35	360
VIII	3	14	47	63	130	37	33	32	358
IX	2	9	38	38	103	25	19	9	243
X	2	2	13	23	55	9	12	4	120
XI	3	1	16	19	41	12	15	13	120
XII	1	12	14	32	39	8	9	5	120

2. *Cycle Length* :

The distribution of cycle length is shown in table 4 & 5 ; Fig 3 & 4 compares the percentage distribution of cycle length before and during medication. The treatment cycle lengths were significantly longer when compared to the premedication cycles. However there was no statistically significant difference between the different lengths during the course of treatment.

TABLE 4

Cycle Lengths (Days)

Cycle	No. of Cycles.	Longest Cycle.	Shortest Cycle.	Mean.
I	393	45	28	33.4
II	371	44	25	30.9
III	353	44	25	29.3
IV	351	42	24	30.5
V	356	41	20	30.5
VI	351	44	20	29.3
VII	347	45	22	30.5
VIII	241	48	22	30.7
IX	120	45	21	30.2
X	120	42	21	30.6
XI	120	41	18	28.6
Total		43.8	22.4	30.3

TABLE 5

Distribution of Cycle Lengths

Cycle	Cycle Length (Days)								
	15—19	20—24	25—29	30—34	35—39	40—44	45—49	50 +	Total
	Number of Cycles								
Before Admis.	0	68	339	153	1	—	—	1	562
I	3	21	75	150	78	47	13	6	393
II	10	27	88	151	61	2	5	5	371
III	21	29	90	159	42	7	1	3	352
IV	13	20	87	175	27	23	3	3	351
V	6	20	90	189	33	15	0	3	356
VI	16	23	94	179	26	6	4	2	350
VII	5	21	79	206	31	11	0	3	347
VIII	3	18	65	146	6	2	1	2	243
IX	0	8	31	64	8	4	0	0	120
X	1	7	31	60	10	6	0	1	120
XI	1	17	52	37	7	1	1	0	120

3. *Amount of menstrual Flow :* (Table 6, 7, Fig V)

The percent distribution of the amount of menstrual flow before and during treatment is given in table 6. The amount of flow was moderate in 80.5% of the total cycles, but the incidence of light flow decreased from 19.6% on admission to 4.19% in the total cycles and the incidence of heavy bleeding increased from 10% before medication to 12.4% in the total cycles. This contributes an important difference between the conventional combined pills and the pill-a-month.

In the conventional combined pills the incidence of scanty flow is reported to be in the region of 72% after 3-4 years of use (Kamal and Hefnawi 1968).

4. *The Duration of Menstrual Flow :* (Table 8, 9 Fig VI VII)

The average duration of menstrual flow of the participants before medication was 4.3 days the duration of flow during treatment is shown in table 8.

TABLE 6

Amount of Monstrual Flow

	Amount of Flow				
	Light	Moderate	Heavy	Amenorrhoea	Total
	Number of Cases				
Before treatment	118	345	137	—	600
Cycle Ia	11	45	15	—	71
Ib	37	413	36	5	486
II	28	329	47	43	447
III	21	305	45	22	393
IV	15	296	42	21	374
V	17	295	38	17	367
VI	13	303	41	9	366
VII	13	312	36	5	365
VIII	10	314	34	3	361
IX	9	208	25	1	243
X	3	103	14	—	120
XI	2	91	27	—	120
XII	1	86	33	—	120

TABLE 7

Per Cent Distribution of the Amount of Menstrual Flow, before and during Treatment

	Amount of Flow			
	Light	Moderate	Heavy	Amenorrhoea
Before treatment	19.6	70.4	10.0	—
Cycle Ia	15.6	64.0	20.4	—
Ib	7.0	86.0	7.0	1.0
II	5.0	70.0	15.2	9.8
III	7.9	76.0	10.8	5.3
IV	4.6	79.0	12.0	5.4
V	5.7	78.0	10.6	5.7
VI	3.5	82.0	12.0	2.5
VII	3.5	85.0	9.7	1.8
VIII	2.95	87.0	9.8	0.15
IX	3.5	86.0	10.45	0.05
X	2.3	86.0	11.7	—
XI	1.5	76.0	22.5	—
XII	0.9	71.5	27.6	—
Total	4.19	80.5	12.71	2.6

TABLE 8

Duration of Menstrual Flow (Days)

Cycle	No. of Cycles	Longest Duration	Shortest Duration	Mean
I	558	18	1	4.7
II	472	19	1	5.7
III	393	20	1	6.2
IV	374	20	2	6.4
V	367	20	1	8.2
VI	366	21	2	6.9
VII	365	19	2	6.6
VIII	361	20	1	6.8
IX	243	15	1	6.1
X	120	20	1	5.9
XI	120	15	1	6.1
XII	120	19	2	7.2
Total	3858	18.8	1.3	6.4

TABLE 9

Distribution of the Duration of Flow

Cycle	Duration (Days)						
	1—3	4—5	6—7	8—9	10—11	12 +	
	Number of Cases						
Before Admis.	184	263	114	39	—	—	Total
I	164	216	56	16	13	10	472
II	77	173	70	28	33	20	401
III	76	137	75	36	30	22	371
IV	63	124	82	30	31	26	353
V	68	100	83	30	28	46	350
VI	64	104	88	40	30	31	357
VII	59	101	106	29	39	26	360
VIII	55	106	100	48	23	29	358
IX	29	84	77	24	20	9	242
X	28	32	29	13	13	5	120
XI	19	33	37	16	10	5	120
XII	20	28	31	16	20	5	120

5. *Intermenstrual Bleeding* :

The incidence of inter menstrual bleeding in the different treatment cycle is shown in table 10. Intermenstrual bleeding was much less with the continuation of treatment so that none of the women who continued to cycle 10 had any such bleeding.

TABLE 10

Incidence of Intermenstrual Bleeding

Cycle	No. of Cases.	1st. week		2nd. week		3rd. week		1, 2, 3			
		Sp.	Bl.	Sp.	Bl.	Sp.	Bl.	Sp.	Bl.	Total	%
Ia	96	—	—	—	—	—	3	—	—	3	4.2
Ib	504	—	—	18	5	12	3	—	15	55	13.8
II	472	—	—	—	2	—	10	—	18	30	7.9
III	393	—	—	—	—	—	8	—	20	28	7.5
IV	373	—	—	—	3	—	3	—	20	26	7.0
V	367	—	—	—	—	—	5	—	15	20	5.5
VI	366	—	—	—	5	—	—	—	14	19	5.2
VII	365	—	—	—	—	—	5	—	10	15	4.1
VIII	361	—	—	—	—	—	2	—	9	11	4.5
IX	243	—	—	—	—	—	3	—	2	5	4.2
X	120	—	—	—	—	—	—	—	—	—	0.0
XI	120	—	—	—	—	—	—	—	—	—	0.0
XII	120	—	—	—	—	—	—	—	—	—	0.0
Total		—	—	18	15	12	42	—	123	212	5.0

6. *Amenorrhoea* :

The percentage incidence of «amenorrheic cycles» is shown in table 11. The incidence of amenorrhoea sharply dropped after the 5th cycle.

7. *Dysmenorrhoea* :

The incidence of dysmenorrhoea increased gradually from 10% before medication to 20% at the 9th cycle. It was mainly in the form of premenstrual congestive pain.

TABLE 11

Incidence of Amenorrhoea

Cycles.	No. of Cycle Amenorrhoeic.	Percentage.
Ia	0	0.0
Ib	5	1.0
II	43	9.8
III	22	5.3
IV	21	5.4
V	20	5.7
VI	9	2.5
VII	5	1.3
VIII	3	0.83
IX	1	0.41
X	0	0.0
XI	0	0.0
XII	0	0.0
Total	129	2.6

This is proved not to be pregnant.

II.—WEIGHT CHANGES

Analysis of the records of the 100 patients who completed 12 cycles reveiled no statistically significant change in their weight all through the period of medication when compared to their premedication weight.

III.—EFFECT ON LIBIDO

There was no significant change in the number of sexual intercourse per week which was taken as a criterion of libido.

IV.—EFFECT ON THE BREAST

No breast changes were found on clinical examination in all cases.

V.—SIDE EFFECTS

The incidence of the various side effects experienced by the women during treatment is shown in table 12. Nausea and vomiting were the main complaints of women. They occured in 6.95% of the whole cycles. They were more frequent in the first few cycles and their incidence decreased rapidly from 30.4% in the first cycle to 1.5% in the 6th cycle.

TABLE 12

The Incidence of Side Effects Per Cent

Cycle	No Symptoms	Nausea	Vomit-ting	Headache	Discharge	Fatigue	Backache	Loss of Hair	Dizzi-ness
	Percent of Cases								
	87.8	—	—	8.2	2.3	1.7	—	—	—
I	3.7	15.4	15.0	14.8	1.9	11.6	4.2	—	0.1
II	40.0	13.0	10.3	13.8	4.2	12.7	4.2	—	1.8
III	58.0	10.4	5.0	7.5	5.73	8.6	4.7	—	0.02
IV	69.0	5.7	1.2	5.5	6.2	7.4	4.0	—	0.48
V	82.0	3.6	—	3.1	3.8	5.1	1.8	—	0.25
VI	90.0	1.6	—	2.1	2.9	4.0	0.5	—	—
VII	92.0	0.26	—	1.8	2.4	1.8	0.54	—	—
VIII	95.0	0.26	—	1.6	0.5	1.3	0.26	—	0.26
IX	99.0	0.25	—	0.25	0.25	0.25	—	—	—
X	92.0	1.6	—	2.5	1.6	2.5	—	—	—
XI	94.0	1.0	—	—	3.0	2.0	—	—	—
XII	93.0	1.6	—	—	3.0	2.4	—	—	—
Total	81.45	4.4	2.6	4.6	3.02	4.1	1.6	—	0.2

Headache was the second main complaint. It occured in 4.57 of total cycles. Its incidence was 14.8% in the first cycle and dropped to 2.1% in the 6th cycle. Fatigue was the 3rd complaint. It occured in 4.05% of total cycles. Its incidence dropped from 11.6% in first cycle to 1.8% in the 7th cycle. Discharge occurred in 3.02% of total cycles. Its incidence increased in the last cycles.

Not a single case got thrombosis during the following period.

VI.—EFFECT ON LACTATION

Lactation stopped completely in 56.6% of cases after the 1st pill, while in 23.4% Lactation was adversely affected necessitating supplmentation. At the end of the 3rd cycle out of the 106 lactating women, only one was still breast feeding, and by the 4th cycle all cases stopped lactation.

VII.—PREGNANCIES

Twenty one pregnancies occured in 3858 cycles. 13 of them occured in the first cycle ; one in the 4th cycle ; 5 in the 5th cycle and one in each of the 6th and 9th cycles. If we exclude the 13 pregnancies which occured in the first cycle where the pill-a-month was not yet effective, the remaining 8 pregnancies occuring in 3334 cycles are considered as a drug failure giving a pregnancy rate of 2.8/100 women/year.

VIII.—DROP OUTS

The drop out rate was highest (21.3%) in the first cycle, it was cut down gradually to 4.8% in the 3rd cycle and 0.26% in the 8th cycle. None of the cases dropped out after the 8th cycle, when they became acclimatised to the drug.

The main causes of drop out were nausea and vomiting (31.2%), bleeding (15.6%) and headache (5.4%).

IX.—ENDOMETRIAL PICTURE

Premenstrual biopsies were taken in 65 cases before therapy and repeated in cycle 1, 3, 6 and 12. In the first cycle, 7 cases showed secretory endometrium. By the 3rd cycle, all biopsies were proliferative.

This points out to an anti-ovulatory effect of the pill-a-month after the first cycle.

The response of the endometrium was not always harmonious. Mixed types were present in 13% in Cycle III.

In this series no evidence of endometrial malignancy was detected. This goes with other reports that not a single case was recorded to develop endometrial carcinoma in pill-a-month users.

X.—CERVICAL SMEARS

Cervical smears did not show any malignant or suspicious cells.

DISCUSSION

The acceptability of the once a month pill was very high. The simplicity of the method is probably its main advantage, it suits illiterates who constitute a lot of those needing contraception in Egypt. This high acceptability is shown by the number of admissions to the trial. Ninety per cent of all attendants to the family planning clinic during the study period requested the pill-a-month.

The pill proved to be effective in preventing pregnancy. Twenty-one pregnancies occurred in 3808 cycles. More than half of the «13 pregnancies» occurred during the first cycle. This was due to the patient failure to follow the instruction of using an additional mechanical contraceptive during that month, where the pill-a-month was not yet fully effective. Eight pregnancies in 3334 cycles can be considered as a drug failure giving an incidence of 2.8/100 women year. This was almost the experience of Maqueo Topete (1969) who reported a pregnancy rate of 2.0/100 women year. In the experience of Guiloff (1970), a rate of 4.0/100 women year was given. Kerrins reported a rate of 5.7/100 women year, Cano (1970) and Larranaga (1970) gave a rate of 1.0 and 1.6/100 women year respectively. Rubio (1970) did not report any pregnancy. This might be due to the progestogen which he added during the first few months of his trial.

We started by giving the pill on the 25th day according to the experience of Greenblatt (1967). To avoid giving the pill to already pregnant women, this group was chosen from those previously fitted with I. U. D's. This combination was not acceptable to most of the cases and this affected the attendance rate, so we shifted to another regimen of administration which was found more suitable. This was to give the pill on the first day of a spontaneous menstrual flow and to combine it during the first cycle with an additional local contraceptive in the form of phenyl mercuric acetate foamy vaginal tablets.

The second pill was given after 21 days so that withdrawal bleeding would correspond with the time of the expected menses. The subsequent pills were given on a fixed date of the calendar month irrespective of the onset of menses.

In the second group «Group B», we followed the same schedule of Maqueo Topete and Guiloff (1970).

Larranga (1970) gave the first pill on whatever day of the cycle the patient was seen. He had the opinion that if a woman was not started on a contraceptive method at her first visit to the clinic, she would not return or if she did, she might be pregnant. Since the liability of pregnancy from the start cannot be excluded by simple clinical examination, 11 of his cases were already pregnant before giving the drug. Beside, irregularities of the cycles were more pronounced in his cases.

The interval between taking the pill and the onset of flow varied from 6-15 days in 80.4% of the cycles. Larranaga (1970) got a tendency towards longer interval, up to 20 days. Rubio (1970) and Cano (1970) reported similar results. There was no statistically significant difference between these intervals in the different cycles, except during the first cycle in Group A, where there was a statistically significant difference at the 1% level. The changes in the menstrual pattern were well tolerated by most of women. We arbitrarly consider a menstrual cycle as regular so long its duration fluctuated between 24 and 35 days. In 74.9% of the total cycles in this trial, the cycle length ranged between 24-35 days. But there was a slight shift towards prolongation of cycle lengths.

A cycle length of 25-29 days was the commonest length in the cases before admission (60%). During treatment, the length was prolonged by about 5 days so that the highest incidence of cycle lengths (48%) was 30-34 days. This was also the experience of Larranaga (1970) and Rubio (1970) ; the incidence of cycles over 34 days in their results was 1.0% and 5.9% before the treatment and after the treatment it reached 16.6% and 16.7% respectively.

The mean length during subsequent cycles in this trial was nearly the same with no statistically significant difference.

Most of those having heavy flow did not report an increase in the amount of blood loss during the use of the pill.

Larranga (1970) and Rubio (1970) experienced similar results except that the incidence of heavy bleeding dropped in Larranga's cases from 19% on admission to 13% during treatment. There was a great difference in the amount of flow during the first cycle in Group A and Group B. The incidence of heavy bleeding was 20.4% in Group A and 7% in Group B. This might be due to giving a high cestrogen dose to a primed endometrium in Group A while in Group B, the pill was given to an endometrium which has already started to be shed out. On the other hand, the incidence of intermenstrual bleeding was much higher in Group B than in Group A due to the withdrawal effect of the progestin part. There was no statistically significant difference in the amount of bleeding during the subsequent cycles.

The duration of flow varied between 2 to 7 days in 77.4% of the cycles. In Larranaga's (1970) and Rubio's (1970) cases, the duration was 3 to 7 days in 81.9% and 93.3% respectively, and it showed a

tendency towards prolongation. This is slightly longer than the duration of a normal menstruation and significantly longer than encountered with conventional contraceptives. Intermenstrual bleeding including spotting occurred in 3% of all cycles in this trial. Its incidence was higher in Group B, specially in the first cycle and dropped rapidly from 11.6 in the first cycle to 1.3 in the 7th cycle. Rubio (1970) got a higher percentage of intermenstrual bleeding reaching to 24.6% in the 3rd cycle. Kerrins (1970) reported an increasing incidence of intermenstrual bleeding from 6.3% in the 2nd cycle to 8.1% in the 6th cycle. In Kerrins' cases spotting was frequent. Its incidence did not drop with the continued use of the pills in subsequent cycles. The incidence of amenorrhoea varied from one cycle to another. It dropped from 9.8% in the 2nd cycle to 0.15% in the 6th cycle. No amenorrhoea occurred in the cycles that followed. In Kerrins' cases, it was 24.2% in the first cycle and dropped to 1.4% in the 7th cycle. In Larranaga's cases, it was 8% in the 2nd cycle and dropped to 1.0% in the 7th cycle. The incidence of congestive dysmenorrhoea increased gradually from 8% before medication and reached 20% in the 9th cycle. This can be easily explained by the increasing pelvic congestion related to the continued use of the pill. It was difficult to determine the effect of the pills on libido. In this investigation, the more or less constant frequency of sexual relation was interpreted as an indirect evidence that no changes in libido occurred after the long term use. None of the published reports discussed this point. The main side effect was nausea and vomiting, particularly during the first 3 cycles. Their incidence was much lowered during subsequent cycles. Nausea occurred during the first few days following ingestion of the pill. This was expected due to the high oestrogen content of the pill. In all studies, nausea was a frequent complaint in a large percentage of women (Kerrins, (1970) ; Cano, (1970) ; Larranaga, (1970) ; and Rubio, (1970).). In our study, nausea started within 24 hours after ingestion of the pill. This may point to the fact that it is central in origin and not due to local gastric irritation. Participants were advised to take the pill at bed time. It is thought that combining an anti-emetic to the pill may help to reduce this side effects. Larranaga (1970) reported the presence of leucorrhoea in 84.0% in the first cycle, then it dropped to 3% in the 7th cycle, while Rubio (1970) gave an incidence of leucorrhoea of 26.2% in the first cycle then 5.9% in the 5th cycle. Cano (1970) who was studying private cases did not report this symptom. In this trial, there was a slight increase in the number of cases complaining of leucorrhoea. 1.0% of the cases in the first cycle com-

plained of it, and this reached 3% in the 12th cycle. It was the main complaint in this cycle.

No statistically significant change in weight occurred in our cases. This was also the experience of others (Kerrins, 1970 ; Larranaga, 1970 ; Rubib, 1970 ; and Cano, 1970).

In the group of lactating women (106 cases) they stopped completely lactation at the end of the 4th cycle. In the first cycle 56.6% stopped lactation, 23.4% supplemented their babies, while 20% continued to nurse their infants. The experience of others was reported as inconclusive although their observation suggested that the period of lactation was shortened by this high oestrogenic medication. So, it is advised not to give it to puerperal lactating women.

The drop out rate was highest in the first month, 17.5% and it was mainly due to nausea and vomiting, but it dropped to zero in the 9th cycle. So when the case was acclimatised to the drug, no drop outs occurred. The simplicity of the schedule of administration was an achieving factor for continuing the medication. The irregular bleeding was not an important factor in the drop out, in contrast to Larranaga's cases (1970) where the menstrual problems constituted the second main cause of withdrawal.

Endometrial biopsies revealed a change from secretory activity into a proliferative one. This took place in a period of 3 months, by the first month 15.5% were still secretory while 84.5% were proliferative. By the 3rd month, 13.0% were mixed but mainly proliferative, while 87.0% were proliferative. On the 6th and 12th months, all proved to be proliferative. This points to an anti-ovulatory effect, besides the response of the endometrium was not always harmonous. Mixed types were present in 13.0% in Cycle III. Cystic dilatation with endometrial hyperplasia was present in 7.1% in Cycle III and 7.2% in Cycle VI and 6.5% in Cycle XII.

These findings compare to those of Maqueo Topete (1968), Rubio and Larranaga (1970), and Guiloff (1970) who reported that endometrial biopsies taken at least 3 months after starting the medication were proliferative. These biopsies were taken after cessation of bleeding and before the next dose of quinestrol-quingestanol. Not a single case was found to develop endometrial carcinoma. Also in all other studies, none reported this complication. In all our attendants a careful examination was done to the lower limb to exclude the

presence of varicose vein. In the subsequent visits, any symptoms like cramps, pain or cedema of the legs sudden severe migraine or unusual headache, sudden onset of severe chest pain or visual disturbance were searched for. Not a single case developed thrombosis of the lower limb. All other studies (Maqueo Topet ; Guiloff 1970 ; Larranaga, 1970 ; Rubio, 1970 ; and Kerrins, 1970) did not report presence of cases with thrombosis of the legs.

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