ONE YEAR TRIAL WITH AN INJECTABLE CONTRACEPTIVE (DELADROXATE)

by

Prof. M. KARIM, M.Ch. ; A. R. AMMAR, M.Ch. ;

S. BADAWI, M.Ch. ; B. A. GANZOURY, M. M.Ch. ;

And

S. ISKANDAR, Ph.D.

Depts. of Obstetrics and Gynaecology and Pathology Ain Shams University

---

The dangers of the increasing population have stimulated the thoughts of different investigators all over the world to invent several forms of contraceptives. The conventional methods of contraception have been largely replaced by th oral pills and intrauterine devices. Several trials have been performed in order to improve these new methods and to minimize their side effects. In the search for an ideal contraceptive, an injectable form has been envented. Felton et al (1965)(1) have enumerated the requisites of a one-a-cycle injectable substance. It should be acceptable to the average woman, inert locally, with minimal side effects, provide absolute pregnancy protection and permit normal resumption of menstrual function and fertility at the conclusion of the course. Several clinical and laboratory studies have been performed (2, 3, 4, 5) on an injectable Progestin-oestrogen contraceptive «Deladroxate»(*) ; they fixed the Progestin dosage and varied the amount of oestrogen in an attempt to obtain an optimum ratio between the two steroids.

The aim of this paper is to evaluate the contraceptive efficiency and safety of one-a-cycle-injectable Progestin-oestrogen contraceptive (Deladroxate). It is composed of 150 mgm. of 16a, 17a dihydroxy-progesterone acetophenide with 10 mgm. of oestradiol enanthate.

---

* Supplied by E. R. Squibb & Sons.

MATERIAL AND METHOD

This work was performed on 27 women attending one of the birth control clinics of Ain Shams University. A complete history was taken from every participant who was subjected subsequently to a thorough general and local pelvic examination. A complete urine analysis, blood picture, Sedimentation rate, Bleeding time, Clotting time, blood urea, blood cholesterol, liver function tests and occasionally Protein-bound Iodine and radioactive Iodine uptake ; were performed to every patient before being admitted to the trial, after the 6th cycle and after the 12th cycle at the end of the trial.

Endometrial biopsies and vaginal smears were obtained before taking the injections, after the 6th cycle and at the end of the work. The patient was instructed to take the 1st injection on the 5th day of her premedicational menses and to visit the clinic every month to report on menstruation, possible side effects and to take the following injection on the 7th—9th day of her menstrual flow. The total number of treatment cycles in our trial was 291.

Analysis of clinical data

Age :

The age of our participants ranged from 20—40 years with an average of 29.7 years. Table I demonstrates the age incidence of our cases.

TABLE I

Age group	—20	21—25	26—30	31—35	35—40	40+	Total
Incidence %	0	29.6	33.4	18.5	18.5	0	100

Parity :

The high fertility of the women is demonstrated by the large number of deliveries, the average Parity was 6.2. Nulliparae and Primiparae did not ask for contraceptives while one third of cases had 4—6 labours. (Table II).

TABLE II

Number of Previous deliveries

No. of Previous deliveries	0	1	2—3	4—6	7—9	10+	Total
Incidence%	0	0	25.9	33.3	29.6	11.2	100

Number of living children

The average number of living children in the trial is 4.3. More than half of the candidates had 4—6 living children (TABLE III).

TABLE III

Number of Living children

No. of Living children	0	1	2—3	4—6	7—9	10+	Total
Incidence%	0	0	33.4	59.1	7.5	0	100

Lactation :

Thirteen women were lactating, an incidence of 48.1%.

Previous contraceptive Methods

Only two women were previously using contraceptives, one was taking the oral pills and the other had an I.U.D.

Past history :

One patient had a past history of thrombophlebitis and varicose veins, a second complained of bronchial asthma and a classical repair was performed to a third.

Side effects :

Table IV demonstrates the various side effects with Deladroxate compared with those present in the Premedicational cycle. It is noticed that the incidence of some of the Premedicational side effects espcially headache, tension, gastric symptoms and sensation of abdominal fullness diminished after Deladroxate medication. No change in libido was observed.

TABLE IV

Comparison between Pre and Postmedicational side effects

Side Effects	H.	T.	G.	N.	D.A.	W.D.	F.	B.F.	A.F.	V.D.
Premedication. % per Cycle	14.8	3.7	11.2	7.4	0.0	3.7	0.0	0.0	11.2	3.7
Post medication. % per Cycle	2.0	0.4	0.4	0.0	1.6	4.0	0.4	0.4	1.1	0.4

H.	= Headache	W.D.	= Weakness, Dizziness
T.	= Tension	F.	= Fatigue
G.	= Gastric	B.F.	= Breast Fullness
N.	= Nervousness	A.F.	= Abdominal Fullness
D.A.	= Depression, Anxiety	V.D.	= Vaginal Discharge

Menstrual Function

Cycle Length :

The average premedicational cycle length was 28.1 days with a range of 22—30 days while the average postmedicational cycle length was 26.1 days with a range of 16—42 days. This shows a slight tendency to shortening of the menstrual cycle. A comparison between Pre-and postmedicational cycle length is demonstrated in Table V. The incidence of normal cycles is diminished on the expense of an increase in percntage of both the short and long cycles.

TABLE V

Comparison between Premedicational and Postmedicational cycle lengths

Cycle Length	—24	24—31	31—	Total
Premedicational%	7.4	92.6	0.0	100
Postmedicational%	30.6	56.3	13.1	100

Table VI, and Figure I show a more detailed analysis of the Postmedicational cycle length in 258 treatment cycles. It is noted that 102 cycles have a normal range (25—30 days). Twenty three cycles were excluded as the flow did not appear and therefore considered ammenorrhaeic cycles, an incidence of 8.2%.

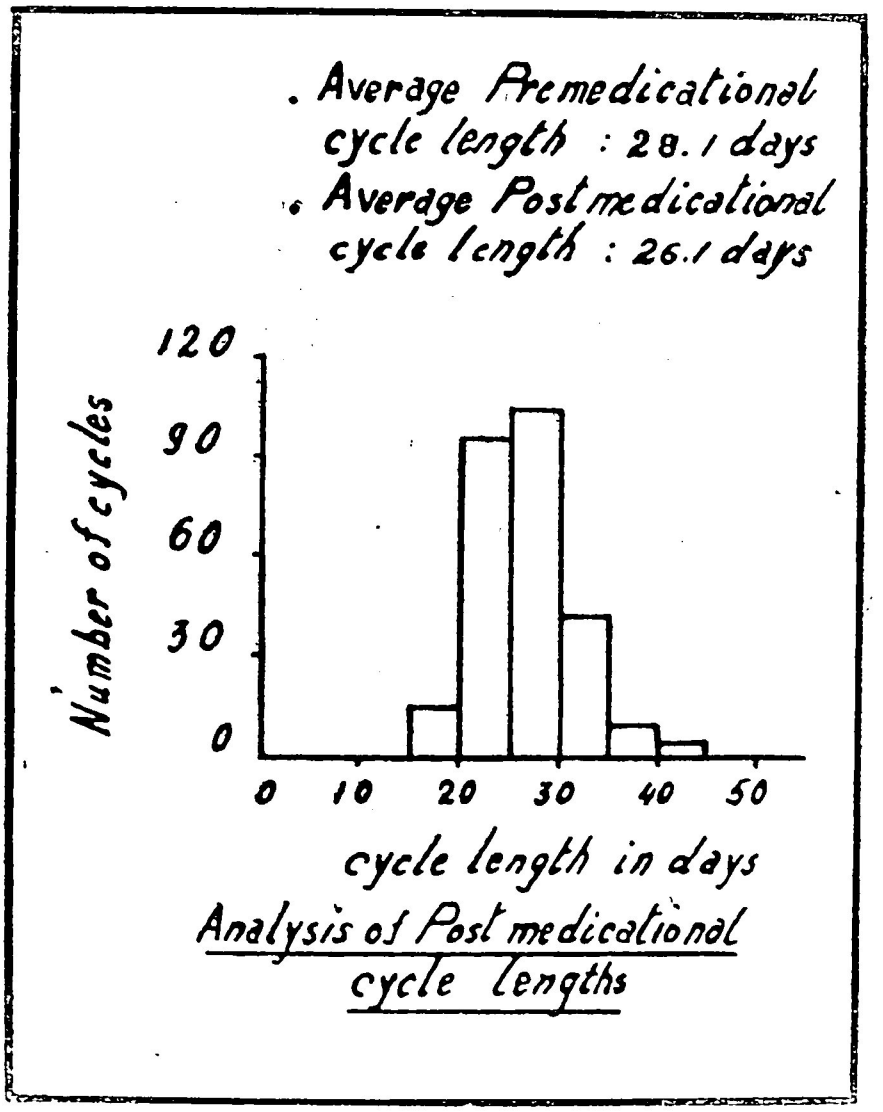


TABLE VI

Analysis of Postmedicational cycle length

Cycle Length	-5d.	5-10	10-15	15-20	20-25	25-30	30-35	35-40	40-45	45+	Total
Cycles	0	0	0	12	92	102	40	10	2	0	258
No. of Cycles	0	0	0	12	92	102	40	10	2	0	258

The average length of the menstrual cycles before therapy and in the different treatment cycles is demonstrated in Table VII and Fig. II. It is shown that it is shorter in the earlier than the later months of the trial.

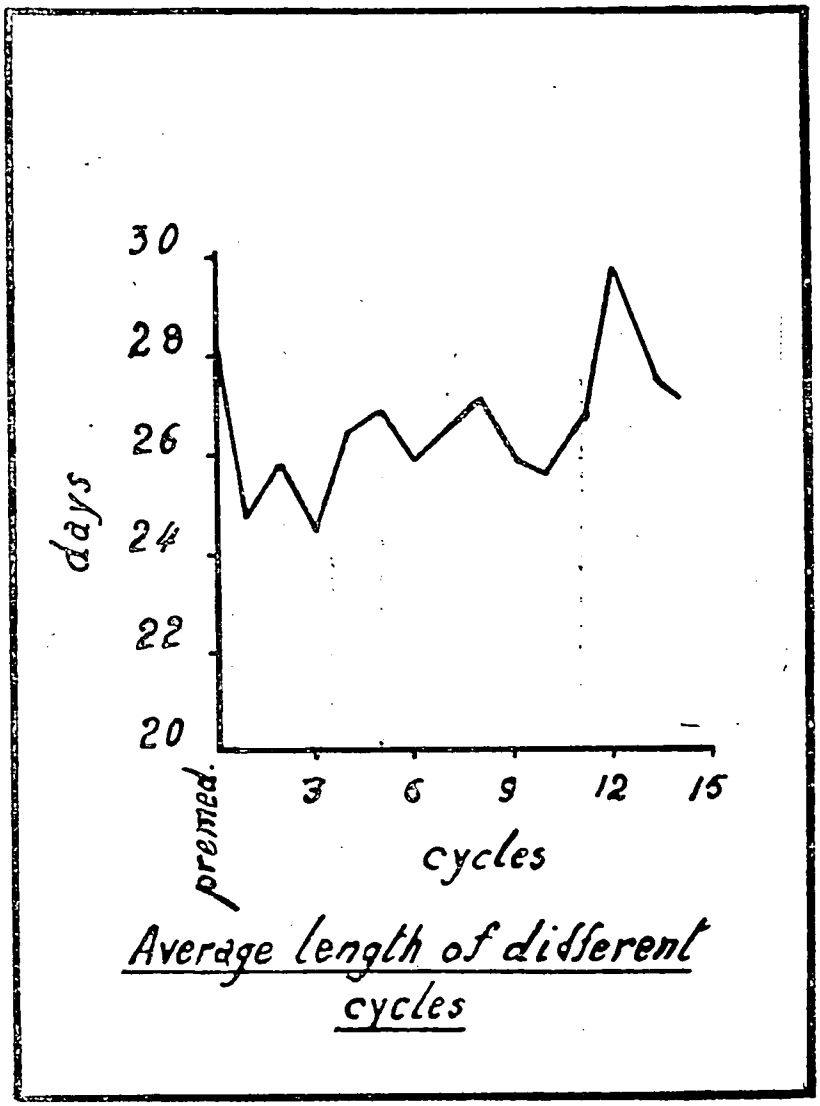


TABLE VII

Average length of different cycles

Cycle	Prem.	1	2	3	4	5	6	7
Average Length	28.1	24.6	25.7	24.2	26.4	26.9	25.7	26.4

Cycle	8	9	10	11	12	13	14
Average Length	27	25.9	25.7	26.5	29.7	27.5	27

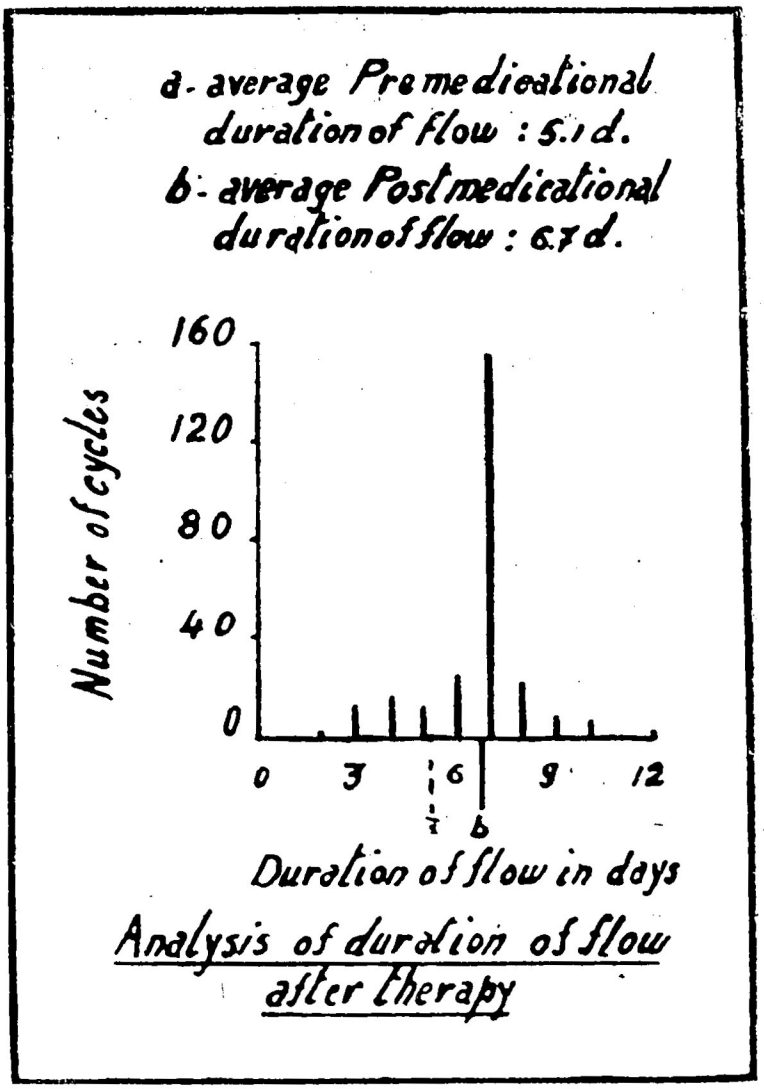
Duration of Flow :

The average Premedicational duration of flow was 5.1 days with a range of 3—8, while the average Postmedicational duration of flow was 6.7 days with a range of 2—12 days. This demonstrates a slight increase in the duration of flow after the injections. Table VIII, and Fig. III show a detailed analysis of the duration of flow after Deladroxate. Most of the menstrual periods (152) lasted for 7 days.

TABLE VIII

Analysis of Postmedicational duration of flow

Duration of flow/ days	1	2	3	4	5	6	7	8	9	10	11	12	Total
No. of Cycles	0	11	12	17	14	22	152	23	8	7	0	2	258



Analysis of duration of flow after therapy

Amount of Flow :

The amount of flow is not materially affected by Deladroxate. There is slight diminution in incidence of Moderate flow while the percentage of scanty loss is slightly increased. Percentage of heavy loss slightly decreased (Table IX).

TABLE IX

Percentage amount of Flow

Amount of Flow	Scanty	Moderate	Heavy
Premedicational %	0	88.9	11.1
Postmedicational %	8	81.2	9.8

Breakthrough bleeding :

Was noticed in 6.1% of cycles. It took the form of spotting that persisted for a few days in 2.2%. Breakthrough bleeding throughout the whole cycle was noticed in 3.9%, it was moderate in 2.8% and Heavy in the rest. It was annoying that the patient did not respond to simple curative methods and the best haemostatic method in such cases was the next injection.

Menatrual Pain :

The incidence of Dysmenorrhea, at the beginning of the trial was 48.1% ; it diminished markedly after therapy to 2.5%. Midmenstrual pain was noticed in 0.3% of treatment cycles.

Weight changes

In three patients, the weight did not show any variation (11.1%). A decrease in weight was noticed in 51.8% (14 patients) and an increase in 37.1% (10 patients). An analysis of the cases that showed a decrease in weight is demonstrated in Table X. About one quarter of the candidates showed a decrease in weight averaging 1—3 pounds.

TABLE X

Analysis of cases that showed a decrease in weight

Average decrease in weight/1bs.	Less than one 1b.	1—3	4—6	7—9	10 or more
%	7.4	25.9	11.1	3.7	3.7

TABLE XI

is an analysis of cases that showed an increase in weight

Average increase in weight/1bs.	Less than one 1b.	1—3	4—6	7—9	10 or more
%	11.1	11.1	11.1	3.8	0

Dropouts :

There were four dropouts. A withdrawal rate of 14.9%. Two of them withdrew because of Haemorrhage which took the form of severe breakthrough bleeding that persisted throughout the whole cycle in one and menorrhagia in the second. The third patient woved away, while the fourth did not continue due to sensation of severe weakness which was the same reason she stopped the pills for.

Laboratory Investigations :

All the results of investigations performed on the patient either before, during or after therapy were within the normal range. The bleeding time, clotting tim and liver function tests were not affected even with the patint that gave hisory of previous thrombophlebitis. The cholesterol level, however, showd a universal diminution after therapy but was still within the normal range.

Endometrial biopsy and Vaginal smear :

Endometrial biopsies from fifteen patients were examined. The curettings were taken Premedicationally and at different dates after the start of the last menstrual period and consequently, also at different dates after the last Deladroxate injection in various cycles, the longest being 13 months. Some of them, for instance, were taken in the first week of the cycle, others in the second week and still others in the third or fourth wek. All the cases taken premedicationally were com pletely normal excluding two cases of chronic endometritis ; all biopsies taken Postmedicationally showed variable degrees of proliferative changes indicating predominance of the oestrogenic effect of the contraceptive drug. Proliferative activity was most remarkable in the Premenstrual phase particularly in patients with delayed periods. In some of these cases, the endometrial picture mimics that of early cystic glandular hyperplasia. Breakthrough bleeding was noticed in 6 patients, 3 of whom, also, showed evidence of chronic endometritis. However, in no case was there any malignancy. Vaginal smears taken from 20 patients were also examined. All of them showed oestrogenic effect but no changes either suggestive or conclusive of malignancy.

DISCUSSION

Clincal experience with the combination of 150 mgm 16a, 17a dihydroxyprogesterone acetophenide and 10 mgm oestradiol enanthate has proved its efficiency as inhibitor of ovulation. No unwanted pregnancy hes occurred in our participants in the period of study which has extended for one year. Our candidates were selected of the younger age groups, 33.4% were between 26—30 years and were highly fertile, 33.3% had 4—6 previous pregnancies.

Side effects were minimal and it is interesting to note that many of the premedicational side effects have disappeared after the start of the trial. The incidence of premenstrual tension has dropped from 3.7% to 0.4%, indicating the efficiency of gestagens in the managemen of Premenstrual tension syndrome.

Menstrual function, however, has been altered to some extent by the use of injections. The incidence of normal cycles is diminished on the expense of an increase in the percentage of both long and short cycles. About one third of cases have a cycle length below 24 days. The cycles were shoter in the earlier than the later months of treatment. The amount of flow was not matrially affected by Deladroxate. There was only a slight increase in the incidence of scanty menstrual flow. This is in contrast with the pills where diminution in the amount and duration of flow is a common complaint. Breakthrough bleeding was, however, noticed in 6.1% of cycles. It was annoying to those patients when it persisted throughout the cycle and it was the cause of withdrawal of two patients.

The endometrial picture was persistantly proliferative irrespective of the time of the cycle when it was taken, showing a predominant oestrogenic effect of the drug. No changes suggestive or conclusive of malignancy were noticed in the endometrium nor in the vaginal smears.

Except for a slight lowering of cholesterol level, still within the normal range, there were no changes in the results of the different laboratory procedures performed. Our findings as regards the endometrial picture and cholesterol level favours a predominant oestrogenic effect of Deladroxate as oestrogens lower cholesterol level. Injectable forms of contraception have the advantages of simplicity of use, obviate the disadvantages of missing pills and the side effects of I.U. D's.

SUMMARY

1. The trial was performed on 27 women for one year.

2. The contraceptive efficiency of the drug was 100%.

3. Side effects were minimal.

4. There was some tendency to shortening of the cycles no material effect on duration or amount of flow, reduction of menstual pain, while breakthrough bleeding was noticed in 6.1% of cycles.

5. Endometrial biopsies revealed a persistantly proliferative activity indicating a predominant oestrogenic effect of the drug.

6. Except for a slight lowering of the cholesterol level, no obvious change in the different laboratory results were noticed.

7. There were four dropouts, two of them due to heavy breakthrough bleeding the other two dropped out for reasons not connected with the medication.

REFERENCES

1. FELTON, H. T. ; HOELSCHER, E. W. ; SCWARTZ, D. P. ; Fertil. and Steril. 16 : 665, 1965.

2. REIFENSTEIN, E. C. ; PRATT, T. E. ; HARTZELL, K. A. ; SHAFER, W. B. ; Fertil. and Steril. 16 : 652 1965.

3. RZKALLAH, T. H. ; TAYMOR, M. L. ; Am. J. Obst. Gyne. 94, 2, 161, 1966.

4. RUTHERFORD, R. N. ; BANKS, A. L. ; COBURN, W. A. ; Paper presented at the 20th Annual meeting of the American Society for the study of Sterility, Miami, Fla., May 15—17, 1964.

5. TAYMOR, M. L. ; PLANCK, S. ; YAHIA, C. ; Fertil. and Steril. 15 : 653, 1964.