LOW DOSAGE GESTAGENS IN FERTILITY CONTROL

by

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INTRODUCTION

Searching for the ideal method to administer steroidal antifertility agents we used-in the present study-a progestogen in low dosage by the non-stop method of administration.

We selected chlormadinone acetate (6-Chloro-6-Dehydro-17-a-Acetoxyprogesterone), a very powerful progestational steroid (as was chown by Clauber-McPhail test) which is devoid of any oestrogenicity (evidenced by the vaginal smear test in castrated rats and by the uterine weight test in immature rats), having no anabolic, androgenic or corticosteroid activities.

MATERIAL & METHOD OF STUDY

(on 0.5 mgm daily dose)

The work was carried out in Galaa Hospital and in the University Hospital Mansoura Faculty of Medicine. Cases were chosen from women attending the family planning clinic, mostly of the low income group. All were of proved fertility. As the effect on milk secretion was one of our targets, some lactating cases at the time of the experiment were included.

Before administration of the pills, a thorough history and clinical examination were performed. Liver function and blood coagulation tests were done in 7 women. Five intelligent non lactating women were chosen for pregnanediol estimation. A double estimation was done in the first and the second half of each of 17 cycles.

The effect of 0,5 mg daily dose on the cervical mucus was found to be constant throughout the 24 hours. Therefore women were instructed to take the tablets at bed-time. It was made clear to them that the tablets should be taken daily regardless of any bleeding or menstruation.

The tablets were supplied freely in monthly packets to assure return of the patients for a monthly questionaire, examination and investigations.

Endometrial biopsies were studied in 22 women, cervical mucus in 48 and post-coital tests in 26 women.

In 19 women, the radioactive iodine uptake of the thyroid gland was estimated before and six months after administration of the tablets.

Oral glucose tolerance tests were done in 10 women before starting the tablets and at monthly intervals.

The husbands of women that completed six cycles were questioned as regards abnormal behaviour or their wives during therapy.

The trial was done on 101 women and included 954 cycles.

TABLE (1)
Distribution of Cases According to age

18—24	25—29	30—34	35—39	40 years and above
12	15	30	34	10

(all had a recent delivery within 3 months).

TABLE (2)
Indications for Contraception

Birth spacing		14
Birth control		79
Medical indications		
Pulmonary T. B.	1	
Diabetes	2	8
Eclampsia	1	
Caesarian section	2	
Rheumatic heart	2	

TABLE (3)

Distribution of Cases According to Number of living Children

One child	2	3	4	5	6 and more
4	8	15	14	28	32

TABLE (4)

Previous Contraception and Method

No Previous contraceptlon	Pills	I. U. D.	Local Chemical.
42	52	4	3

TABLE (5)

Frequency of Sexual Intercourse Per Week

2—3 times	More frequent	Less frequent
72	11	18

RESULTS

No pregnancies were recorded during administration of the pills. Up to the time of writing this report the method has proved to be 100% effective in preventing pregnancy despite the fact that 4 women admitted missing one or more tablets during therapy.

The side effects were practically absent. In only one patient, continuous bleding compelled us after 16 days to stop the medication and switch to combind therapy.

We met with 20 drop outs after 1—8 cycles. The reasons were not investigated.

TABLE (6)

side-effects

Side-effects	No. of women	% of cycles
Headache	6	1.6
Giddiness	18	5
Nausea	8	1.5
Vomiting	—	—
Distension	2	1
Breast discomfort	1	0.2
Discharge	—	—

TABLE (7)

Menstrual Changes

Regular menses Throughout treatment		Alternating amenorrhoea with regular menses		Amenorrhoea throughout treatment	
Normal menses	52	Missing 1 cycle	8	Duration of experiment	
(a) previously normal	43	Missing 2 cycle	5	2 months	5
(b) » hypomenorrhoea	4	Missing 3 cycle	2	2 months	1
(c) » menorrhagia	5	Missing 4 cycle	2	6 months	1
Hypomenorrhoea	1	Missing 6 cycle	3	8 months	3
Menorrhagia	5				
Total	58	Total	20	Total	10

13 women had one cycle and were excluded.

Among amenorrhoeic cases 17 were lactating.

TABLE (8)

Spotting and Breakthrough Bleeding

No. of cycles	No. of patients	% of cycle
1	20	
2	1	
More than 2	2	
Total	23	4.7

TABLE (9)

Duration of Menstruation in Days

Average duration before	Average duration during
4.2	4.2

TABLE (10)

Dysmenorrhoea

Relieved	Developed	Not relieved
6	2	4

TABLE (11)

Premenstrual tension

Developed	Relieved
2	1

TABLE (12)

Effect on Lactation ϕ

Total No.	Lactation unaffected	Lactation diminished
34	32	2

ϕ lactating women started the pills within 2 months after labour.

TABLE (13)

Weight Changes

No change	Changes within 2 kg.	Gained more than 2 kg.	Lost more than 2 kg.
17	59	9	3

TABLE (14)

Changes in Libido

No change	Improved	Diminshed
99	2	—

TABLE (15)

Effect on Pre-existing Diseases

Disease	No. of patients	Effect
Allergic dermatitis	1	No effect
Bronchial asthma	1	No effect
Thrombophlebitis	1	No thromboembolic accidents
Diabetes	2	No change in insulin requirement.

Hair loss was a complaint in one patient.

Liver function tests and blood coagulation tests as well as glucose tolerance showed insignificant variations. One patient developed infective hepatitis during therapy and refused our advice to stop the medication, liver function tests were studied during illness and 6 weeks after recovery. The latter were found normal.

None of the husbands noticed abnormal behaviour of his wife during therapy.

Endometrial biopsies : 128 biopsies were studied. Sixty eight were obtained in the first half of the cycle. Forty six showed a proliferative pattern and 22 showed a mixed (proliferative and early secretory) pattern. Sixty biopsies were taken in the second half of the menstrual cycle. Twenty three showed a full secretory, eight were poor secretory, seven showed a mixed and 22 showed proliferative patterns. Proliferative patterns constituted 37% of biopsies obtained in the second half of the cycle. The epithelium did not show atrophic changes not uncommon with the combined therapy. In some proliferative sections, secretory subnuclear vacuoles were observed in the epithelial lining of the glands. In all biopsies the stroma was congested, oedematous and showed focal areas of haemorrhages.

Pregnanediol estimation : In 13 cycles the double estimation showed differences suggesting ovulation. Only in 4 cycles (about 24%) the differences suggested anovulation.

Cervical mucus : The cervical mucovs was studied in 48 women in the first half. of the mcnstrual cycle in 288 cycles. In nearly all specimens it was scanty, thick, viscid and opaque with diminished thread obility (Spinnbarkeit) and some showed the «tack» phenomenon. Most specimens contained leucocytes. Ferning was absent in 202 specimens, while 86 showed mixed areas of ferning and globule formation.

Post-coital tests : Tests were done on 26 women including 84 cycles from the eighth to the fifteenth day of the cycle. Thirty six cervical mucus specimens showed no sperms, 43 showed non-motile sperms and only in 5 poorly motile sperms were seen. In no case more than 10 sperms per H. P. F. was observed.

Radioactive iodine studies : The thyroid uptake did not show any significant change between the values before and during administration of the pills.

DISCUSSION

Cases included in the study were selected at random. Most of the women were young and highly fertile. Seventy four women were above thirty years, the same number had more than three living children. Seventy nine women presented for birth control and only 14 for birth spacing. Eight women were included because of medical reasons among which were T. B. diabetes, history of eclampsia, caesarian section and rheumatic heart disease. These observations indicate the national family planning programme has not reached the low parity but potentially high fertility group of young women the conviction of whom to practice birth control will contribute materially to the success of the programme.

Nulliparae did not present in the series as there is a strongly held belief among this class that a newly married bride should provide her husband with a child at the earliest opportunity.

Of the 101 women studied, only 42 did not practice contraception at any time before. Fifty two had been at some time or another on oral pills of different combination and dosages. Four women gave a history of I. U. D. insertion and 3 practiced contraception by the use of local chemicals. Other conventional methods such as condom, dutch cap and safe period were not observed as all women were of low educational standard.

A questionaire about the frequency of sexual intercourse revealed that 72 couples practiced it 2—3 times weekly, 11 more than 2—3 times and 18 less frequently.

No pregnancies were observed up to the time of writing this report. Moghni (7) and Martinez-Manautau (8) also reported no failures using 0.5 mg chlormadinone continuously. Rudel (11) reported 13 pregnancies in a series of 945 women all due to missing tablets, a «use effectiveness» pregnancy rate of 2.07%. Martinez-Manautau and Rudel, using 0.5 mg chlormadinone cyclically in 419 women for 1—9 cycles, reported one patient failure. No pregnancies when 0.5 chlormadinone was given by the continuous method (3).

The continuous method of use eliminated the difficulties encountered among the hospital class of women to understand the cyclic method of administration of the combined pills. This method of administration seemed more acceptable to this group of women.

The figures of side-effects encountered are so low compared with any form of combined therapy. No woman complained of vaginal discharge de novo or admitted diminution of libido. Nervous disorders, virilising symptoms and abnormal behaviours were not observed.

Fifty eight women menstruated regularly during administration of the pills. Twenty had alternating amenorrhea and 10 had amenorrhea throughout therapy. Amenorrhea was encountered in 93 cycles that is about 10% of the cycles. This high figure can be explained by the fact that 9 out of the 20 women that had alternating amenorrhea and 8 out of the ten women that had amenorrhea throughout therapy were lactating.

Considering the high incidence of anovulation during lactation, women should not menstruate under continuous therapy as there are no endogenous hormonal fluctuations. Women did not object to amenorrhea specially during lactation.

Spotting and breakthrough bleeding occurred in 23 women, in 20 of whom bleeding was present in only one cycle. The complaint was encountered in 4.7% of the cycles. Moghni (7) gave the incidence as 2.7% of early and 0.4% of late cycles. Martinez-Manautau and Rudel concluded that the continuous low dosage gestagen method for achieving contraception had diminished the side-effects encountered with hormonal pills except irregular bleeding. They reported that with the cyclic method of administration of 0.5 mg chlormadinone 20—25% of women developed spotting and breakthrough bleeding in each of the first three cycles diminishing in subsequent cycles.

With combined therapy, Osman & Darwish (8) reported breakthrough bleeding in 28% of women (10.6% of cycles) using a combination of 2 mg medroxyprogesterone + 0.05 mgm ethinyl oestradiol and in 5% of cycles using a combination of 3 mg chlormadinone + 0.1 mgm. mestranol (Aconcen) (9). Topozada (12) gave the figure as 17.3% of cases and 2.1% of cycles, Behrman (1) as 28.6% of cases and Mears and Grant (6) as 14.1% of cycles.

There was no appreciable effect on the amount of menstruation. Only one woman complained of hypomenorrhea and 5 of menorrhagia. Hypomenorrhea is a side-effect that has a bad psychological effect in our patients and is a frequent cause of «drop out» in patients on combined therapy inspite of reassurance.

The average duration of menstruation was not affected being 4.2 days before and after therapy.

Out of 10 women having dysmenorrhea, 4 were not relieved. This is explained by the irregular inhibition of ovulation.

Only 2 wmen developed premenstrual tension and one was relieved from pre-existing tension.

Inhibition of milk secretion was noticed in only 2 out of 34 lactating women in the series. Inhibition of milk secretion is an important problem in our countery as breast feeding is the most popular way of nursing babies in U. A. R. Many lactating women refuse taking the pills because of the possibility of milk inhibition. Inhibition of milk secretion was complained of in 65% of lactating women using a combination of 2 mg. medroxyprogesterone + 50 mcg. E. E. and in all lactating women using 3 mgm. chlormadinone + 0.1 mgm. mestranol (Osman & Darwish) 9. Rice-Wray reported that about half of all lactating mothers notice a decrease in milk secretion when the combined therapy is used. Chinnatamby[2] in Ceylon using Conovid E noticed that 10% had immediate inhibition of milk secretion and that in 30% lactation did not last more than 4 months. We are convinced with the difficulty of assessing the effect of gestagens on milk secretion. However we believe that milk secretion is almost unaffected by continuous low dosage gestagen administration.

Weight changes were negligible. If we exclude changes within 2 Kgm. only 9 women gained more than 2 Kgm and 3 lost more than 2 kg. The therapy appeared to have no effect on allergic diseases, diabetes, liver function, blood coagulation, glucose tolerance or thyroid function.

The endometrium showed different hormonal patterns, sometimes revealing dissociation between glandular and stromal responses. However, the effect on the endometrial stroma was uniform. Epithelial atrophic changes not uncommon with the combined therapy were absent explaining the unfrequent occurence of hypomenorrhea & amenorrhea in non lactating cases.

Endometrial studies suggested inhibition of ovulation in 37% of cycles while pregnandiol estimations suggested the occurrence of anovulation in 24% of cycles. The latter results need further investigation.

Cervical mucus and post-coital tests showed that chlormadinone in this dosage rendered the mucus hostile to the sperms. Hostility of

the cervical mucus seems to be an important way of action of chlormadinone in this dosage. Is it due to changes in physical or chemical characteristics ? Or is it enzymatic ? Or is it sperm incapactation ? The answer can only be available after further investigations.

Inhibition of ovulation seems to occur occasionally and exact figures are difficult to determine accurately because we did not attempt pituitary gonadotrophin assays. However the occurrence of menstruation inspite of continuous therapy, the absence of atrophic endometrial changes as well as unaffected milk secretion suggest minimal pituitary inhibition.

Histological changes in the endometrium did not seem to be a factor in preventing conception. Other parameters for the mode of action e. g. histochemical and motility changes were not studied.

SUMMARY

1. The administration of 0.5 mg chlormadinone daily by the continuous method is effective in the control of fertility.

2. The side-effects encountered were recorded and found to be less than those of combined therapy except breakthrough bleeding and amenorrhea to which possible explanations were given.

3. The effect on milk secretion was minimal, the method is particularly suitable during lactation.

4. The possible modes of action were discussed.

ACKNOWLEDGMENT

We would like to thank the Scientific Bureau of E. Merck Company in U. A. R. for supplying the samples necessary for the study.

We appreciate the help of F. S. Galal (Dept. Of Radiotherapy, Ein Shams Univ.), S. Azzouz & E. A. Hamid (Supreme Council of Family Planning).

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