EXPERIENCE WITH CHLORMADINONE—MESTRANOL IN CONTRACEPTION A STUDY OF 1286 CYCLES

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The present work was performed to evaluate the effect of chlormadinone, mestranol combination (Aconcen) as a contraceptive, stressing the cardiovascular and electrolyte changes together with the endometrial changes and side effects.

MATERIAL AND METHOD

The study comprised 51 women, randomly selected from those attending the Family Planning Clinic, Cairo University Hospitals. All were multiparae. Their age ranged between a 19 and 42 years. A careful history was taken and a thorough general and pelvic examination was carried out.

Aconcen was given, 21 tablets per month, free of charge. Each tablet is composed of 3 mg. Chlormadinone acetate, (6—chloro—17 hydroxypregna—4, 6—diene—3, 20—dione—17 acetate) together with 0.1mg. mestranol ; (ethinyl estradiol 3 methyl ether).

A monthly followup was carried out for 6—24 months. At each monthly visit any complaint was noted and cases were selected for the cardiovascular, electrolyte and endometrial study.

Fifteen non cardiac cases were subjected to twelve lead conventional electrocardiograms before and at frequent intervals during the period of the study which extended for two years.

The electrocardiograms were analysed in accordance with the accepted standards. The T or U—P line was taken as the base line and the Q—T was corrected to rate by Bazet formulae as modified by Taren and Szilague.

Serum sodium and potassium levels were estimated by the flame photometric method in eight cases, before and six to twelve months after receiving the pills. These investigations ; cardiovascular and electrolyte were always conducted between 26 th—28 th day of the cycle.

A premedication base—line endometrial biopsy was performed in 30 cases in the premenstrual phase. 82 endemetrial specimens were collected during medication. These specimens were arranged so as to spread all through the days of the cycle. In addition 20 specimens were obtained after stoppage of pill use.

The changes in each endomtrial component gland, stroma and blood vessels were described separately. The number of glands per low power field was noted. The diameter of the glands and the height of their cells were measured using a micrometer eye with a graduated slide.

RESULTS

The effectiveness of the compound is documented by the fact that not a single pregnancy occured during the course of treatment, even with missing one or two tablets. The results obtained are better presented under the following headings :

I.—CLINICAL OBSERRATIONS

II.—CARDIO—VASCULAR CHANGES

III.—ELECTROLYTE CHANGES

IV.—ENDOMETRIAL CHANGES.

I.—Clinical Obserrations

A.—Menstrual Patterns

Interval between the end of tablets and onest of flow

This varied between 2 & 10 days with an average of 4.2 days. In 60.8% of the cycles it ranged between 3—5 days. In 27.6% it was less than 3 days and in 11.6% it was more than 5 days.

Amenorrheic cycles, i.e. when menstruation did not start after 7 days from the end of tablets, occured in only 4 cycles during the course of the trial.

Cycle length

This varied between 22 and 34 days with an average of 28.7 at cycle one, 28.9 at cycle 3, 29 at cycle 6 and 29 at cycle 9, 29.8 at cycle 12, 30.2 at cycle 18 and 29.6 at cycle 24. The average for all cycles was 29.2 days (before therapy 28.6 days).

Amount of flow (Judged subjectively)

This was modrate in 56.5% of cycles, excessive in 7.1% and scanty in 36.4%. (Before therapy the figures wefe 70.2, 14.8 and 15% respectively).

Duration of flow

This varied between 1 to 12 days with an average of 4.3 in cycle one, 4.4 in cycle three and six, 4.5 in cycle nine and 4.2 days for the whole cycles. (Before therapy the average was 4.2).

Breakthough bleeeing

Spotting occured in 1.2% and bleeding in 1.6% of the cycles. Both occured mainly in the first three cycles and particularly during the 2nd and 3rd weeks of these cycles.

Dysmenorrhoea

In 78.6 of the cycles no dysmenorrhea was reported. 19.9% of cycles were accompanied by slight or moderate dysmenorrhea while in 1.9% of the cycles dysmenorrhea was described as severe. (Before therapy the incidence was 11.8% and 9.4% respectively).

B.—*Side Effects*

Loss of appetite occured in 9% of the cycles. It was more pronounced in the first three cycles and dropped to 7% in cycle 3 and to zero in cycle 9.

Nausea was experienced in 8.4% of the cycles. This was maximum (27.5%) in cycle one and dropped to zero by cycles 24.

Vomitting, on the other hand, was exmerienced by theree participants only in cycle one, three and six; it did not recur in next cycles.

Gastric discomfort and or abdominal distension was experienced by particpants in 3.9% of the cycles. Both dropped to zero by cycle 9.

Headach occured in 28.4% of the cycles and its incidence was more or less constant throughout therapy.

Cloasma was reported by 6 participants, while acne occured in one case only. fall of hair, however, was complained of in 13.5% of the cycles.

Breast tenderness was reported in 4.5% of the cycles. Increase in size occured in 1.9% and diminution in 12%, while nodularity was not reported by any of the participants.

No change in libido occured in 96.9% of the cases during therapy. Two cases, however, reported an increase in libido, while 3 cases noticed a decrease in their libido.

Weight Changes

An increase in weight occured in 18% of the cases during treatment and a decrease occured in 24.4% . The increase in weight was mainly during the first three cycles so that the participants who continued to add weight after that were only 9% of the cases. A more thorough investigation revealed that the increase in weight was in the range of 0.9 kg./ case during the whole period of treatment.

II.—CARDIO—VASCULAR CHANGES

Apart from a slight elevation of the systolic blood pressure within the range of 10 mm. Hg. no other abnormal symptoms or signs referable to the cardio-vascular system occured during the period of observation. Incidently, no venous or arterial thromboembolic episodes were encountered.

Analysis of the serial electrocardiograms revealed the following :

1. A substantial drop of the heart rate per minute from a mean of 70.5 with S.E. + 1.35 to a mean of 60.5 with S.E. + 1.07. The difference was found to be statistiscally highly significant at the 1% level (T. 4.6 and P/0.01).

2. No significant changes were detected in the amplitude or configuration of the P or QRS weves. The omplitude of the.T weves did not show slight increase in 5 cases (33%).

3. No significant changes were noticed in the P—R interval, the QRS duration of the Q—Tc interval.

III.—Electrolyte Changes

There was a slight rise in serum sodium and a drop in serum potassium levels which were, however, not statistically significant. The following table show the results of the electrolyte changes.

Serum Sodium and Potassium levels before and after therapy

	Potassium level		Potassium level	
	Before	6—months later	Before	6—12 months later
Mean (m.Eg./litre)	139±9	141±16	3 98±0.47	3.8±0.8
S.E. ±	2.25	4	0.12	0.2
P	> 0.5		> 0.5	

IV.—Endometrial Changes

The stroma continued to be stimulated by the oral steroid until it reached a mild pseudodecidual state, while the glands, after an initial stimulation phase, soon failed to keep pace with the continued progestational influence and glandular exhaustion and atrophy occured.

The endometrial cycle during therapy could be roughly divided into three phases ; an initial weak oestrogenic phase, a mild precocious progestational phases and lastly a regressive state dominate the picture.

The average number of gland per low power field were 28 early in the cycle and 12 in the premenstrual days. The glandular size varied from 45.3u to 33u in the cycle. Cell height was no the average 19 u early in the cycle and 13 u in the premenstrual days. The secretory activities appeared rather late in the cycle, their Subnuclear vacuoles reached their maximum incidence in the 11th day of the cycle. Supranuclear vacuoles which were less common and morel irrigular, lasted for a short time in the mid-days of the cycle.

The endometrium returned to its normal state after stoppage of therapy. A delay in ovulation, however, was noted in the immediate three post-cessation cycles.

DISCUSSION

According to the WHO Technical report in 1966, there is no substantia evidence of adverse reactions that accompany the use of oral contraceptives. The same report, however, recommended that the effects of these steroids on the cardio-vascular system, electrolytes, endometrium and side effects needs more investigation.

The menstrual pattern, in this trial was not greatly disturbed in rythm or amount in most of our cases. The only significant change was in the incidence of scanty flow which increased during therapy to 36% compared to 15% before treatment. Breakthrough bleeding occured in 1.6% and spotting in 1.2% of the cycles. This is almost twice the figure given by Block (1968) who reported an incidence of 0.6% in 160 women treated for 2893 cycles. Lubitz (1965) reported breakthrough bleeding in 2 out of 290 cycles.

As regards the side effects, the most outstanding was headache which was complained of in 28Æ of the cycles. This figure is seven times that given by Nevinny-Stickel (1966) who reported the incidence of headache as 4Æ in 295 cycles.

Severe dysmenorrhoea, previously complained of by 9% of participants before therapy dropped to 1.9%.

Weight gain occured in 18% of the cases compared to 63% in Block experience (1968) and 5% in the group treated by Nevinny-Stickel (1966).

It is important to recall that the average increase in weight in our cases after twelve cycles was 0.9 Kg. and that non of the participants discontinued therapy for this cause.

The endometrium under chlormadinone, mestranol therapy revealed the same general features reported before, Grant (1964). Pincus (1965), Mazhar et al (1965) and Tagi (1957). Abnormal stromal cells described by Deckerty et al in 1959 were never observed in our cases. Again glandular arrest, rather than regression described by Morria in 1961 was challanged in our report as well as of others, Goldsieher (1963) rice Wray (1963), Grant (1964) and Anseri, Arronet (1966).

Comparing the endometrial measurements to that reported before (Tagi 1967)) reveals that chlormadinone, mestranol combination appears to be slightly more oestrogenic and henne less progestational than the 19 nor testosterone compounds. Maqueo, Perez-Vaga, Goldzieher et al (1963) found that the morphological pattern induced by chlormadinone acetate is intermediate between the 2 non-steroid nor ethylnodril and norethindrone. It does not cause the marked oedema seen with norethynodril nor it causes the prolonged secretory activity of norethindrone.

The safety of oral contraceptive drugs on the heart was also demonstrated by electrocardiographic recordings before and during receiving the pills. The serial electrocardiograms, did not show any significant change. we were

miticulous in choosing all participants with a haemoglobin level above 11.2grams% to exculude any E.C.G. changes that can be attributed to anaemia (El-Sherif et al., 1964) or its subsequent correction which is said to follow diminution in the menstrual flow caused by the pills. (WHO Technical Report, 1968)).

A significant decrease in the heart rate and an occasional increase in the amplitude of T waves were observed. The different reports on side effects as nausea, headacqe, migraine, altered visual functions, increased appetite, convulsions and depression suggest that oral contraceptives may have an effect on the hypothalamus and other higher centres. This as well as the changes in the amount of siliva secreted per day noticed in many participants (Kamal et al.) arouses the possibility of vigal stimulation as the cause of the radycardia. It may be important to recall here that diminution of ovarian hormones at the menopause is often associated with opposite effects namely vasomotor and functional cardio-vascular disturbances such as hot flushes, sweatin palpitation and tachycardia.

The absence of abnormal T wave changes and of any alternation in the Q—T_c excludes the possibility of a toxic effect on the cardiac muscle. The T wave which represents ventricular recovery and the Q—T interval are very sensitive indices to any alteration in the physiology of the cardiac muscle. Many drugs are frequently reported to cause its flattening or inversion (Treidberg 1966). The slight increase in the amplitude of the T waves can be attributed to the slowing of the heart rate.

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