

# EFFECT OF CONTINUOUS LOW DOSAGE (0.5 MG.) CHLORMADINONE ACETATE ON THE GENITAL TRACT OF WOMEN

by

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## Introduction

In recent years interest has been directed to continuous low dose progestin compounds because of their different mode and site of action. A study was therefore undertaken on Chlormadinone Acetate 0.5 mg. to evaluate its antifertility effect in relation to changes produced on the genital tract. A study of vaginal cytology, endometrial histology and post-coital tests were carried out for the same.

## Material and Methods

Chlormadinone Acetate (0.5 mg.) was given continuously to 200 women for its antifertility effect over a period of two years for 1512 cycles.

Vaginal smears were taken at the first visit before starting the therapy and repeated at 6-12 monthly intervals. Endometrial biopsies were performed at 6-12 month intervals. Most of these were obtained in the premenstrual period though a few were taken during the first and second week of a menstrual cycle. The post-coital tests were done during the mid-cycle. The clinical effects of the drug are discussed elsewhere.

The women were in the reproductive age group and of proved fertility. Eighty women were having lactational amenorrhoea.

## Results

**Vaginal Cytology:** Vaginal smears were taken in 133 patients before starting

the drug. The smears were repeated at 6-12 months intervals in most of these patients. The smears were stained by Papanicolaou and Shorr's techniques. The Karyopyknotic Index (K. P. I.) and the degree of clumping of the cells were assessed in all smears. Progestational effect with tendency to form groups and clumps were seen all throughout the cycle. No abnormal smears were found.

MacDonald *et al* (1968), have also indicated that smears taken during the mid-cyclic phase (10-16th day) of regular cycles showed distinct progestogenic effects.

Fig. 1 shows the mean Karyopyknotic Index of smears taken during different days of the cycle. It shows a curve with low values at the beginning and at the end of the cycle and a plateau round about mid-cycle. It resembles the curve of a normal menstrual cycle, with a difference, that the Karyopyknotic Index is low throughout compared to a normal cycle.

**Endometrial Histological Changes:** A total of 110 biopsies were taken during this study at various intervals in the menstrual cycle, 96 during the premenstrual phase and the remaining 14 biopsies were taken during early part of the cycle. The different endometrial patterns in 96 pre-menstrual biopsies are shown in Table I. Forty-eight showed normal secretory changes. Fig. 2 showed irregular secretory changes; 10 showed inactive endometrium and in 26 atrophic endometrium was obtained. Thus, 50% of the

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Received for publication on 13-4-1972.

TABLE 1  
Endometrial Histological Change

Endometrial Patterns	No.
Normal secretory	48
Irregular secretory	12
Inactive	10
Atrophic	26
Total	96

latory women (Fig. 3).

The histological pattern in biopsies described as irregular secretory, showed glands with mild degree of convolutions, lined by low columnar epithelium and scanty or absent secretion in the lumen. The glands were of variable shape, size and tortuosity. Some glands were small. oval or round with scanty secretions. Stroma was edematous. Stromal cells were swollen and many dilated sinusoids were noted (Fig. 4).

biopsies taken during the premenstrual phase showed histological pattern similar to that found in normal non-treated ovu-

In the inactive endometria (Fig. 5) the

FIG. 1  
RHYTHMIC INDEX OF VAGINAL SMEARS DURING DIFFERENT DAYS OF MENSTRUAL CYCLE.

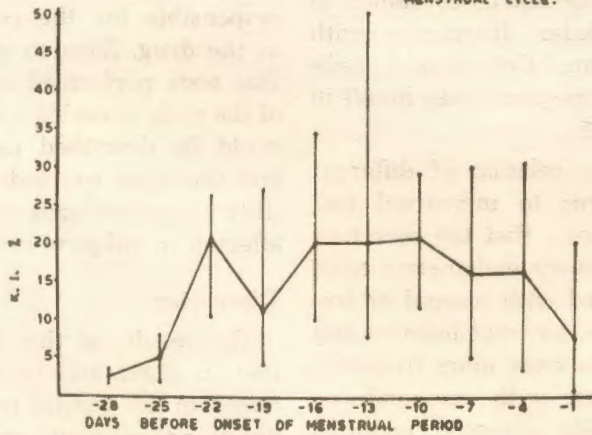
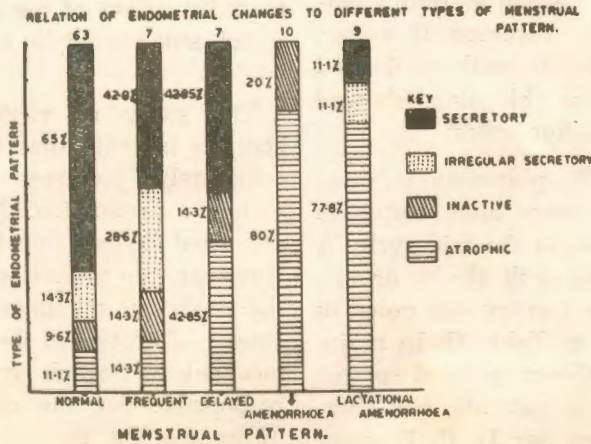


FIG. 2  
RELATION OF ENDOMETRIAL CHANGES TO DIFFERENT TYPES OF MENSTRUAL PATTERN.



glands looked exhausted and were lined by cuboidal epithelium. They were fewer in number, small, round or oval in shape with no secretions. The stromal appearance was variable. In some cases a compact dense stroma was seen and in others stromal edema and larger stromal cells were present. In 26 cases atrophic endometrium was obtained. Here, very scanty tissue containing only blood and mucus or very thin stromal tissue with few broken up glands were seen. The uterine mucosa felt very smooth to the curette in those patients. Mears *et al* (1969) found no evidence of endometrial atrophy in her study and all specimens contained at least some glandular fragments with columnar epithelium. Considerable individual variation of response was found in endometrial biopsies.

Fig. 2 shows the relation of different endometrial patterns to menstrual patterns. It clearly shows that the secretory and irregular secretory endometria were commonly associated with normal or frequent menstruation, whereas inactive and atrophic endometria were more frequently noted in subjects with amenorrhoeic cycles. Occasionally atrophic endometrium was obtained in patients with normal secretory menstrual cycles. Zanartu *et al*, (1968) found normal secretory pattern in the majority of women. However, he found that subjects with prolonged or irregular uterine bleeding showed signs of inactive endometrium.

**Post-coital Test:** The post-coital test was carried out 10-12 hours after coitus in 67 patients round about the mid-cycle. A thick cellular mucus with absent or low Spinnbarkeit and no ferning was noted in all cases as shown in Table II. In majority of specimens, absent or dead sperms were found. In three patients, few sluggishly motile sperms per L. P. F. were

TABLE II  
*Results of Post-coital Tests During the Midcycle*

Cervical Mucus Spinnbarkeit	Absent or Dead Sperms	Few Sperms Per L.P.F.
Negative	39	1
+	21	2
++	4	-
+++	-	-

obtained. It seemed that the mucus did not favour adequate sperm penetration and survival of spermatozoa. These changes of the mucus may be particularly responsible for the contraceptive action of the drug. Zanartu *et al*, (1968) found that tests performed between 10-12 days of the cycle revealed sperm motility which could be described as "fair" or "good" and therefore concluded that mucus hostility to spermatozoa was not consistently affected in subjects under this therapy.

#### Discussion

The results of this study indicate that certain alterations or changes were produced in the genital tract of subjects under this therapeutic regime. In what way these changes from normal, by themselves or together, were responsible for the antifertility effect of the drug is a question which still cannot be adequately explained.

The study of vaginal cytohormonal changes indicate that the drug does not completely suppress the endogenous estrogen production. Neither were any abnormal changes noted during this study. However, the progestogenic effect seen in the smears at all times of the cycle indicate an alteration of the normal ovulatory mechanisms which could be partially responsible for the contraceptive effect (Figs. 6 & Fig. 7).

The demonstration of secretory changes in the endometrium in the majority of specimens would suggest the association of ovulatory cycles with this compound. Martinez-Manatou *et al.*, (1967) found 65.3% of the endometria showing normal or irregular secretory pattern and believed that to be indicative of ovulation. However, the 14 biopsies that were taken during the early part of the cycle also showed progesterational changes in our study. It is possible that the endometria here were only reflecting the progesterational effect of the drug and not necessarily the events occurring in the ovary. Further study on the histological patterns of endometrium during the early part of the cycle along with cyclic hormonal studies are indicated. It appears that under this continuous progestin regime for contraception, there is greater variation of histologic appearance of the endometrium than noted with other types of hormonal contraceptives. The morphological changes range from inactive to atrophic to secretory with a fair number of irregular secretory types. The histological appearance had no bearing to the length of therapy.

The demonstration of irregular secretory, inactive and atrophic endometria in women using this drug might be associated with alterations in the biochemical milieu of the endometrium involved in the implantation processes and thus be one of the factors contributing to the antifertility effects of the drug.

The changes in the cervical mucus might also act as a hostile barrier to the survival and passage of sperms through the genital tract. Further studies on the effect of progestogens on the biochemical composition of the cervical mucus are needed for better understanding of this mechanism.

Chlormadinone Acetate seems to produce changes in the physiological reproductive mechanisms which are different from those of the conventional oral contraceptives. Further studies are indicated to understand their significance and implication as regards its antifertility effect.

#### Acknowledgements

The author wish to express their thanks to the Dean, T. N. Medical College and B. Y. L. Nair Hospital for allowing the publication of this data.

This work was supported by a grant from the Indian Council of Medical Research.

The drug was kindly provided by Syntex Pharmaceuticals Limited, United Kingdom.

Grateful thanks are extended to Dr. E. J. deSouza, Professor of Anatomy for taking microphotographs.

Thanks are due to Nair Hospital Research Society for defraying the expenses involved in preparation of slides, illustration, microphotographs and typing of the manuscript, and Mr. K. L. Patel for drawing the illustrations.

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*See Figs. on Art Paper III-IV*