ENDOMETRIAL HISTOLOGY AND PROGESTERONE LEVELS IN WOMEN USING NORETHINDRONE ACETATE IMPLANTS FOR CONTRACEPTION

by

D. Takkar,* D.G.O., M.D.

G. Kinra,** M.D.

S. Jeyaseelan,*** M.B.,B.S.

K. R. Laumas,† Ph.D.

and

V. Hingorani,‡ F.R.C.O.G., F.A.C.S., F.A.C.O.G. (Hony.), F.I.C.S., F.A.M.S.

Introduction

While the contraceptive efficacy of implant-D containing 40 mg of norethindrone acetate is well established (Bhatnagar *et al,* 1975; Laumas *et al,* 1975), its mode of action still remains unknown. Taking into consideration the release rate of norethindrone acetate being approximately 140 ug/24 hours and the fact that serum LH and FSH levels are not affected (Rehman *et al,* 1976), it is suggested that its contraceptive effect may be similar to continuous low dose progestogen pills. It is well documented that these so called 'mini pills' do not suppress ovulation (Martinez 1967) but they bring about the changes in cervical mucus and interfere with sperm migration. They have also been reported (Moghissi and Mark, 1971; Moghissi *et al,* 1973) to cause alteration of the FSH and LH ratio and endometrial histology. Present study was undertaken to investigate the effect of this implant on endometrium and serum progesterone, to throw some light on the mode of its contraceptive action.

Materials and Methods

Twenty women in the age group of 20-40 years and parity 1-5 participated in this study. They had used implant-D for duration of 7-27 months. Their menstrual cycles ranged from 25-30 days. The endometrial biopsies were taken between days 16-28 of the menstrual cycle and on the same day peripheral venous blood was collected for serum progesterone estimations. The endometrium was collected in neutral formaline and was processed for light microscopy. The endometrial dating was done by the criteria of Noyes *et al,* (1950). The serum progesterone levels were measured by radioimmunoassay using antiserum raised against progesterone (11-alphahemiscucinate B.S.A. and 1, 2, 6, 7-3H progesterone) as tracer. The coefficient of variation between and with-

*Asst. Prof. Department of Obstetrics & Gynaecology, AIIMS, New Delhi.

**Senior Research Officer, Dept. of Obst. & Gynec., AIIMS, New Delhi.

***Junior Resident, Dept. of Obst. & Gynec. AIIMS' New Delhi.

†Prof. and Head of the Dept. of Reproductive Biology, AIIMS, New Delhi.

‡Prof. and Head of the Dept. of Obst. & Gynec., AIIMS, New Delhi.

Request for reprints to be sent to Prof. V. Hingorani, Head of the Department of Obstetrics & Gynaecology.

in assay ranged from 6.92 to 12.38 per cent. The values of water and serum blanks were always less than the least detectable dose level which was 25 pg for the lineerised standard curve. The sensitivity of the assay was 2.5 ng/ml serum. The results were calculated using a logit-log transformation on a programmable Hewlett Packard Calculator 9810A (Laumas *et al,* 1974).

Results

Nineteen women showed endometrium in the secretory phase. In all these 19 cases the serum progesterone levels were above 3 ng/ml thus confirming that ovulation had occurred (Saxena *et al,* 1976). In the remaining woman the endometrial biopsy taken on the 26th day of the cycle showed proliferative endometrium and serum progesterone was 2.15 ng/ml. She had been using the implant for 8 months at the time when the biopsy and progesterone estimations were done (Table I). Dating of endometrial biopsies and progesterone levels in relation to duration of use of implants are shown in Table I and Fig. 1-7. The endometrium corresponded to the dating (± 2 days) in 10 women (Fig. 7). In 5 women it was retarded by 3 or more days (Fig. 1). In 4 women it was enhanced by 3 or more days (Fig. 6).

Discussion

It has been suggested that continuous low dosage progestogens may be acting at different sites to achieve their contraceptive effect. They may act by reducing fertility of sperms by the altered cervical mucus or by interfering with sperm capacitation (Oberti *et al,* 1974; Kamran *et al,* 1975; Moghissi and Mark, 1971; Moghissi *et al,* 1973).

Few studies have been done so far on endometrial histology with silastic implants containing progestogens. Croxatto *et al* (1969) reported 30% secretory, 61% irregular secretory and 9% irregularly inactive endometrium in their study with megestrol acetate implants. In another study (Tejuja, 1970) reported secretory endometrium corresponding to the dates in women using 1-3 megestrol acetate implants, while irregular endometrium was obtained from biopsies in women using four megestrol acetate implants. Possibly the degree of changes are associated with the amount of steroid released.

When dating of endometrium was done in this study, it revealed a disparity between stromal, glandular and vas-

TABLE I

Type of Endometrium and Serum Progesterone Levels with Duration of Use of Implant

Duration of Use (Months)	Total No.	Secretory Endometrium	*P_4 Levels (ng/ml)	Proliferative Endometrium	*P_4 Levels (ng/ml)
7- 9	8	7	4.5-10.0	1	2.1
10-12	3	3	6.5- 9.0	—	—
13-15	2	2	10.0-12.0	—	—
16-18	1	1	5.1	—	—
19-21	3	3	3.2-10.0	—	—
22-24	2	2	3.8- 5.1	—	—
25-27	1	1	3.2	—	—

*P_4 = Serum Progesterone.

cular components, in some of the specimens making the dating difficult (Fig. 2). Only approximate dates could be assigned to a particular specimen. An overall impression gathered was that the columner epithelium of the glands was shorter than expected in the normal specimens (Fig 1, 2). The glandular component was less than that of stromal. The stromal cells frequently showed patchy oedema and haemorrhages. The glands were showing less secretions than that expected at the date of cycle when that particular specimen was taken (Fig. 4). Predecidua was usually well marked (Fig. 4). All these changes have been well described by Dallenbach-Hellweg (1971) as the effect of progestogens on endometrium.

The endometrium was corresponding to ± 2 days in 10 women. Of the remaining 10, one was in the proliferative phase (Fig. 5), in 5 it was retarded by 3 or more days (Fig. 1), and in the remaining 4 it was enhanced by 3 or more days (Fig. 6). Kamran *et al* (1975) reported retarded endometrium in 3 women and 2 women had corresponding endometrium, out of 5 subjects who were taking continuous low dose quingestanol acetate.

It could be assumed by this study that norethindrone acetate containing silastic implant-D by and large does not inhibit ovulation and one of the modes of action of its fertility control is by bringing about imbalance in endometrial maturation during the luteal phase.

Summary

The effect of a single implant-D containing 40 mg of norethindrone acetate was studied on the endometrium of 20 women using this method of contraception for 7-27 months, the endometrial dating is correlated with serum progesterone levels. Ovulation was indicated in 19 of them by serum progesterone being more than 3 ng/ml and presence of secretory endometrium, while in one woman the premenstrual endometrial biopsy showed proliferative endometrium and serum progesterone was 2.1 ng/ml. Dating of endometrium was difficult as there was disparity between glandular, stromal and vascular components. It showed retarded endometrium in 5 and enhanced in 4 suggesting thereby that one of the modus operandi of this implant might be through bringing about minor endometrial changes, while ovulation remains uninhibited.

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See Figs. on Art Paper I-II