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# Hormonal profile, endometrial histology and ovarian ultrasound assessment during 1 year of nomegestrol acetate implant (Uniplant®)

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**The present study assesses the endocrinological, endometrial histology and vaginal ultrasound profiles of nomegestrol acetate subdermal implant users at varying times after insertion. Follicle stimulatory hormone, luteinizing hormone, oestradiol, progesterone, vaginal ultrasound assessment of the ovaries and the histological dating of the endometrium were serially assessed for a period of 50 days immediately after the insertion, and after at 6 months and 12 months of use. The endocrinological results of this prospective observational clinical trial indicated that 75% of the cycles across the study period in Uniplant® users were anovulatory, 63% showing development of a persistent non-luteinized follicle. Anovulatory cycles devoid of follicular development were seen primarily in the first months after Uniplant insertion. Ovulatory cycles represented 25% of the Uniplant cycles. Inadequate luteal phase or disregulation of follicular growth was a common feature of ovulatory cycles. In conclusion, these findings suggest that the contraceptive mechanisms of a single nomegestrol acetate subdermal implant involve prevention of follicular growth, development of a persistent non-luteinized follicle, inadequate luteal phase and disruption of the endometrial architecture.**

*Key words:* gonadotrophins/nomegestrol acetate subdermal implants/oestradiol/ovarian function/progesterone

## Introduction

Uniplant® (Theramex, Monaco) is a second generation single silastic implant containing 55 mg nomegestrol acetate with contraceptive effectiveness of 1 year's duration (Coutinho, 1993). The exact contraceptive mechanisms of action of progestogen-only contraceptive implants are not completely understood. Among the principal mechanisms to prevent conception that have been demonstrated in previous studies are alterations in cervical mucus sperm interaction (Croxatto *et al.*, 1987), ovulation inhibition (Faundes *et al.*, 1991), inadequate luteal phase (Brache and Faundes, 1985), and alteration in endometrial development (Shaaban *et al.*, 1993).

In order to understand the endocrine mechanisms that prevent conception in Uniplant users, the endocrinology of follicular development, ovulation and luteal phase were assessed at varying time after the insertion of the nomegestrol acetate subdermal implant. This investigation assessed serum gonadotrophins, oestradiol and progesterone concentrations as well as the vaginal ultrasound profile of growing follicles, and the histological changes of the endometrium, at different stages of the ovarian cycle.

## Materials and methods

### *Subjects*

Twelve volunteers, ages 25–30 years, were recruited among women requesting contraception at the family planning clinic at San Borja-Arriaran Clinical Hospital, National Health Service, School of Medicine, University of Chile, Santiago, Chile. The mean body mass index (BMI) of the subjects was 23.1 ± 1.64 kg/m$^2$ [BMI = weight (kg)/height (m$^2$)]. Each subject had a haemoglobin concentration >12 g/l, was not lactating and had not used any hormonal contraception in the previous 3 months. Subjects were similar in parity and all had regular menstrual cycles of 26–34 days.

Each subject was able to understand and willing to comply with the study protocol and provided signed and informed consent which was approved by the Institutional Review Board.

### *Study design*

The clinical trial was a longitudinal study of 12 healthy women during the use of one year of a nomegestrol acetate subdermal contraceptive implant. The insertion of the implant was performed on days 3–5 of the menstrual cycle. Ovarian function in each subject was then prospectively evaluated using transvaginal ultrasound (Aloka 630 5MH2 vaginal probe, Tokyo, Japan) and serum luteinizing hormone (LH), follicle stimulating hormone (FSH), oestradiol and progesterone concentrations. The ultrasound and hormonal assessment were performed every other day for three study periods during the use of the implant. Study A was conducted for the period of the first 45–50 days after insertion, study B between days 180 and 220 and study C between days 310 and 360 after the insertion.

Two women dropped out of the research protocol at the fourth and fifth month after Uniplant insertion respectively. The first subject requested implant removal for irregular bleeding and the other subject was unable to attend the clinic every other day. She continued to use the contraceptive method and participated in the multicentre clinical trial of acceptability and efficacy of the subdermal implant.

### *Control cycle*

The control group consisted of nine healthy women, with regular menstrual cycles, who were not using any hormonal contraceptive method. They had similar clinical characteristics to the Uniplant users. The control menstrual cycles were assessed following the same protocol as the Uniplant users.

### *Radioimmunoassays*

Blood samples (3 ml) were obtained as reported in the study design. The serum was stored at –20°C until analysis. LH and FSH were measured in duplicate by radioimmunoassay using NIADDK reagents as previously reported (Devoto *et al.*, 1989). Values were expressed as mIU/ml using LER 907 as the standard. The intra-assay and inter-assay coefficients of variation (CV) were 7 and 8% respectively. Measurement of oestradiol and progesterone was performed with the reagents provided by the Matched Reagents Programme for Radio Immunoassay, Human Reproduction Programme of the World Health Organization. The intra-assay coefficients of variations for oestradiol and progesterone were 11 and 8% respectively. Values were expressed in pg/ml or ng/ml. The conversion factor to SI units pmol/l for oestradiol and nmol/l for progesterone are 3.6 and 3.2 respectively.

### *Statistical analysis*

The relationship between follicular diameter and oestradiol biosynthesis was established by using linear regression correlation curves.

The transverse mean for LH, FSH, oestradiol and progesterone was calculated from 24 samples throughout the same study period. The length of each study period was 50–53 days and samples were obtained every other day. A total of 24 samples was thus available per subject in each study period.

The differences between groups and separate phases of the study periods were assessed by ANOVA and by two-tailed unpaired *t*-test.

All values were expressed as the mean ± SEM; $P$ values $<0.05$ were considered significant.

### *Endometrial biopsy*

The endometrial samples were obtained by pipelle biopsy (Unimar, Wilton, CT 06897, USA). Each endometrial biopsy was prepared by standard methods for light microscopic assessment with haematoxylin and eosin staining.

Histological assessment of the endometrium was performed in six Uniplant users at different stages of their ovarian cycle.

A total of two biopsies from the Uniplant users and one biopsy from each control subject was taken.

The dating of the endometrial biopsy was evaluated for progestational effect and the histological date assessed by the criteria of Noyes *et al.* (1950).

## Results

Three distinct patterns of ovarian activity and endocrine profile were observed during Uniplant use. A total of 12 subjects was available for investigation in period A, and 10 each for periods B and C. Each subject could be characterized as developing one of three patterns in each of the study periods: (1) absence of follicular activity (12%, 4/32), (2) development of a persistent non-luteinized follicle, without evidence of ovulation (63%, 20/32), or (3) ovulatory cycles (25%, 8/32). The prevalence of each pattern varied in each study period and is described in Table I. Anovulation (patterns 1 and 2), and especially the absence of follicular activity (pattern 1), was more common in study period A. Ovulatory cycles (pattern 3) were not observed during study period A, and were more common with prolonged Uniplant use. The development of a non-luteinized follicle without ovulation (pattern 3) was noted in all study periods. Representative examples of each endocrine and ultrasonographic profile, with menstrual patterns, are demonstrated in Figure 1.

**Table I.** Distribution of ovarian activity during the use of Uniplant

| | Study period A | Study period B | Study period C | Total outcome (%) |
|---|---|---|---|---|
| Number of subjects | 12 | 10 | 10 | 32 |
| Absence of follicular activity | 3 | 0 | 1 | 4 (12.5) |
| Persistent non-luteinized follicle without ovulation | 9 | 6 | 5 | 20 (62.5) |
| Ovulatory cycles | 0 | 4 | 4 | 8 (25.0) |

Panel A is representative of a subject devoid of follicular activity. Clinically, this subject presented with oligomenorrhoea and gonadotrophin concentrations in the range of the early follicular phase of the menstrual cycle (LH 8 mIU/ml, FSH 5 mIU/ml). Vaginal ultrasound and serum oestradiol assessment demonstrated the absence of follicular activity.

Panel B is representative of a subject who developed a persistent non-luteinized follicle without evidence of ovulation. Follicular development is clearly represented by a progressive increase in serum oestradiol concentrations as well as by the progressive growth of a leading follicle as demonstrated by vaginal ultrasound. In this subject the FSH/LH ratio was $>1$, and no LH or FSH surge followed the progressive increase of oestradiol. No increase in serum progesterone was noted.

Panel C is representative of a subject who ovulated during the use of Uniplant. Follicular collapse of the leading follicle (22 mm) was noted after a progressive increase in oestradiol and coincident with an LH surge. An increase in serum progesterone was noted after follicular collapse, suggesting an active corpus luteum with steroidogenic activity.

### *Endocrine and ultrasound findings in anovulatory cycles*

Table II shows two patterns of anovulation during the study (patterns 1 and 2). Subjects with pattern 1 had a maximum follicular diameter that ranged from 4 to 10 mm with an average maximum follicular diameter of 9.5 ± 0.02 mm. Maximum oestradiol concentrations ranged from 35 to 64 pg/ml with a mean of 56 ± 8. Progesterone concentration ranged from 0.25 to 0.39 ng/ml. The mean LH/FSH ratio was 0.87. Subjects with pattern 2 had a maximum follicular diameter that ranged from 33 to 50 mm with a mean of 48 ± 4, which was significantly larger than that for subjects with pattern 1 ($P < 0.05$). Maximum oestradiol concentrations ranged from 196 to 688 pg/ml with an average of 206 ± 40, which was also significantly greater than the oestradiol concentrations in subjects with pattern 1 ($P < 0.05$). The LH/FSH ratio was 0.97. Progesterone concentrations ranged from 0.20 to 0.45 ng/ml and were not significantly different from subjects with pattern 1.

### *Comparison of ovulatory cycles during the use of Uniplant to normal ovulatory cycles*

Overall, ovulation was noted in 25% (8/32) of cycles during Uniplant use. The ovulatory cycles were present only after 6

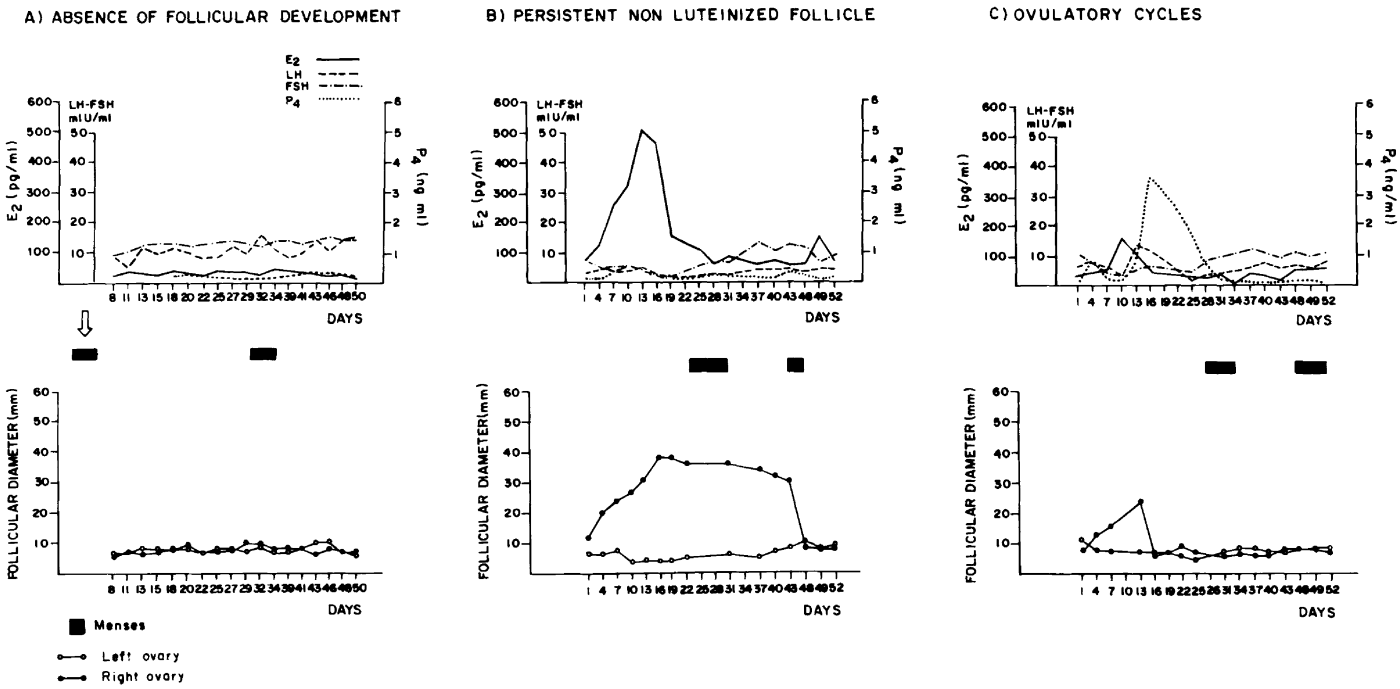


**Figure 1.** Individual endocrine [oestradiol ($E_2$), luteinizing hormone (LH), follicle stimulating hormone (FSH) and progesterone (P)], follicular diameter as determined by vaginal ultrasound and menstrual profiles of three Uniplant users who developed: (**A**) absence of follicular development, (**B**) persistent non-luteinized follicle and (**C**) ovulatory cycles.

**Table II.** Comparison of endocrine and ultrasound assessment of ovarian activity in anovulatory users of Uniplant. The maximal follicular diameter (mm), the maximal oestradiol ($E_2$) concentration (pg/ml) and the transverse means of luteinizing hormone (LH), follicle stimulating hormone (FSH), $E_2$ and progesterone (P) are given in four cycles of women devoid of follicular development and 20 cycles of women who developed a persistent non-luteinized follicle

| | Study period A | Study period B | Study period C |
|---|---|---|---|
| No. of subjects | 12 | 10 | 10 |
| **Absence of follicular development** | | | |
| *n* | 3 | 0 | 1 |
| Max. follicular diameter (mm) | 9.5 ± 0.5 | – | 10 |
| Max. $E_2$ value (pg/ml) | 57 ± 15.6 | – | 71 |
| Tx. LH (mIU/ml) | 10.5 ± 0.6 | – | 7.8 ± 0.4 |
| Tx. FSH (mIU/ml) | 12.1±1.2 | – | 9 ± 0.5 |
| Tx. $E_2$ (pg/ml) | 56 ± 8 | – | 45 ± 4 |
| Tx. P (ng/ml) | 0.3 ± 0.05 | – | 0.3 6± 0.03 |
| **Persistent non-luteinized follicle** | | | |
| *n* | 9 | 6 | 5 |
| Max. follicular diameter (mm) | 40 ± 3* | 48 ± 4 | 50 ± 6* |
| Max. $E_2$ value (pg/ml) | 416 ± 58* | 521 ± 56 | 416 ± 76* |
| Tx. LH (mIU/ml) | 8.9 ± 1.3 | 5.8 ± 1 | 5.5 ± 0.05 |
| Tx. FSH (mIU/ml) | 8.9 ± 0.5 | 6.7 ± 0.5 | 5.7 ± 0.8 |
| Tx. $E_2$ (pg/ml) | 171 ± 45* | 201 ± 26 | 246 ± 36* |
| Tx. P (ng/ml) | 0.37 ± 0.05 | 0.25 ± 0.02 | 0.4 ± 0.06 |

Tx = transverse mean.
Data are means ± SEM, ANOVA and unpaired *t*-test.
*Values which are significantly different between the two groups of anovulatory women ($P < 0.05$).

months of Uniplant use. The ultrasound and endocrine characteristics of these cycles were compared to nine spontaneous ovulatory cycles of controls, as shown in Table III. The maximum diameter of the leading follicle in users of Uniplant ranged from 24 to 30 mm with an average of 29 ± 0.4, which was significantly larger than the average maximum diameter in the ovulatory cycles of control subjects ($P < 0.05$). The maximum serum oestradiol concentration ranged from 203 to 467 pg/ml with an average of 350 ± 52, which was also significantly greater than the average maximum oestradiol in controls ($P < 0.05$). The

**Table III.** Comparison of endocrine and ultrasound assessment of ovarian activity between ovulatory users of Uniplant and normal ovulatory cycles. The maximal follicular diameter, and the serum concentrations of luteinizing hormone (LH), follicular stimulating hormone (FSH) and oestradiol ($E_2$) at the periovulatory stage are given. Area under the curve (AC) for progesterone (P) and $E_2$ is shown during the luteal phase

| | Control | Uniplant |
|---|---|---|
| Total no. of subjects | 9 | 32 |
| Ovulatory subjects | 9 | 8 |
| Max. follicular diameter (mm) | 19.5 ± 0.2 | 29.0 ± 0.4[a] |
| Max. LH (mIU/ml) | 87.8 ± 7.5 | 16.3 ± 2[a] |
| Max. FSH (mIU/ml) | 24.6 ± 3.3[a] | 10.46 ± 0.9[a] |
| Max. $E_2$ (pg/ml) | 208 ± 38 | 350 ± 52[a] |
| AC of luteal $E_2$ | 243 ± 87 | 246 ± 35 |
| AC of luteal P | 14.04 ± 5.5[a] | 8.95 ± 1.82 |

Data are means ± SEM unpaired *t*-test.
[a]Values which are significantly different from control values ($P < 0.05$).

area under the curve (AC) of luteal progesterone in subjects using Uniplant was significantly lower than control subjects (8.95 versus 14.04, $P < 0.05$). No difference was noted in the AC of luteal oestrogen between Uniplant users and controls.

### *Characteristics of follicular growth and oestradiol secretion*

The relationship between follicular diameter and oestradiol secretion during follicular growth in Uniplant users who developed persistent non-luteinized follicles (A), in Uniplant users who ovulated (B) and in normal subjects (C) is shown in Figure 2.

A linear correlation between oestradiol concentration and follicular diameter (mm) was present in Uniplant users who developed a persistent non-luteinized follicle ($n = 20$, $r = 0.75$), and in those who ovulated ($n = 9$, $r = 0.85$). Control subjects ($n = 9$) showed a slightly higher degree of linear correlation ($r = 0.89$).

The assessment of the growth rate of the leading follicle was evaluated every 48 h, according to the criteria of Doody *et al.* (1987). Growth rate was similar in Uniplant users who developed persistent non-luteinized follicles, Uniplant users who ovulated, and control subjects.

The relationship between follicular diameter, oestradiol secretion and time in subjects who developed a persistent non-luteinized follicle is shown in Figure 3. A linear correlation between oestradiol concentration and follicular diameter (mm) was noted for the first 18–20 days. Thereafter a significant drop in oestradiol secretion was observed ($P < 0.05$), in spite of the persistence of the follicle as visualized by ultrasonography.

### *Endometrial histology*

The histology of the endometrium in Uniplant users at different phases of their ovarian activity is illustrated in Figure 4.

In Uniplant subjects devoid of follicular activity, the endometrial glands were small and lined with low cuboidal epithelial cells (Figure 4A). The stroma did not show a decidual reaction.

In Uniplant subjects with a persistent non-luteinized follicle, the endometrium demonstrated a predominance of progesterone-dependent features (Figure 4B). Endometrial glands were tortuous and with glandular secretion. The stroma was oedematous and the vessels showed periarteriolar stroma cuffing.

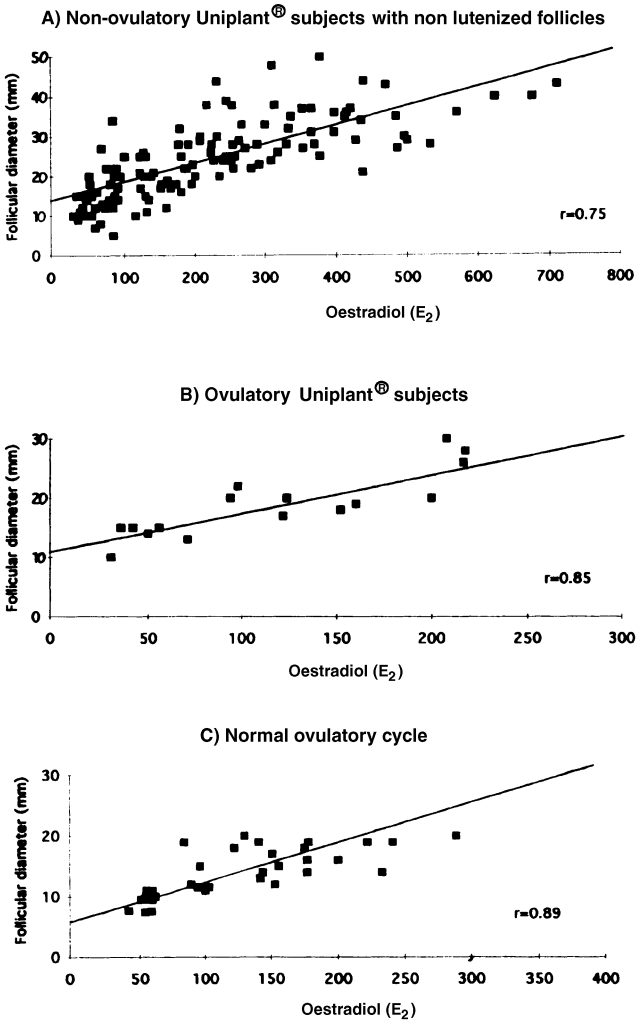


**Figure 2.** Linear correlation between oestradiol ($E_2$) concentration and follicular diameter in subjects using Uniplant and control women.

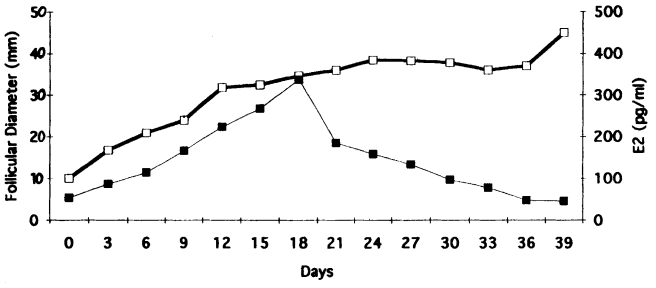


**Figure 3.** Relationship between follicular diameter, oestradiol ($E_2$) concentration and time in Uniplant users who developed persistent non-luteinized follicle. Open squares represent ultrasound measurements, black squares represent serum $E_2$ concentrations.

In Uniplant subjects at the time of breakthrough bleeding, the endometrial glands were unevenly distributed, narrow and contained atrophic epithelium (Figure 4C). Stroma cells were dense with abnormal vascular changes. Thromboses and ectasia of the vessels suggested an irregular shedding of the endometrium.

In Uniplant subjects who ovulated, a biopsy was taken on day 26 of the menstrual cycle. The endometrial dating

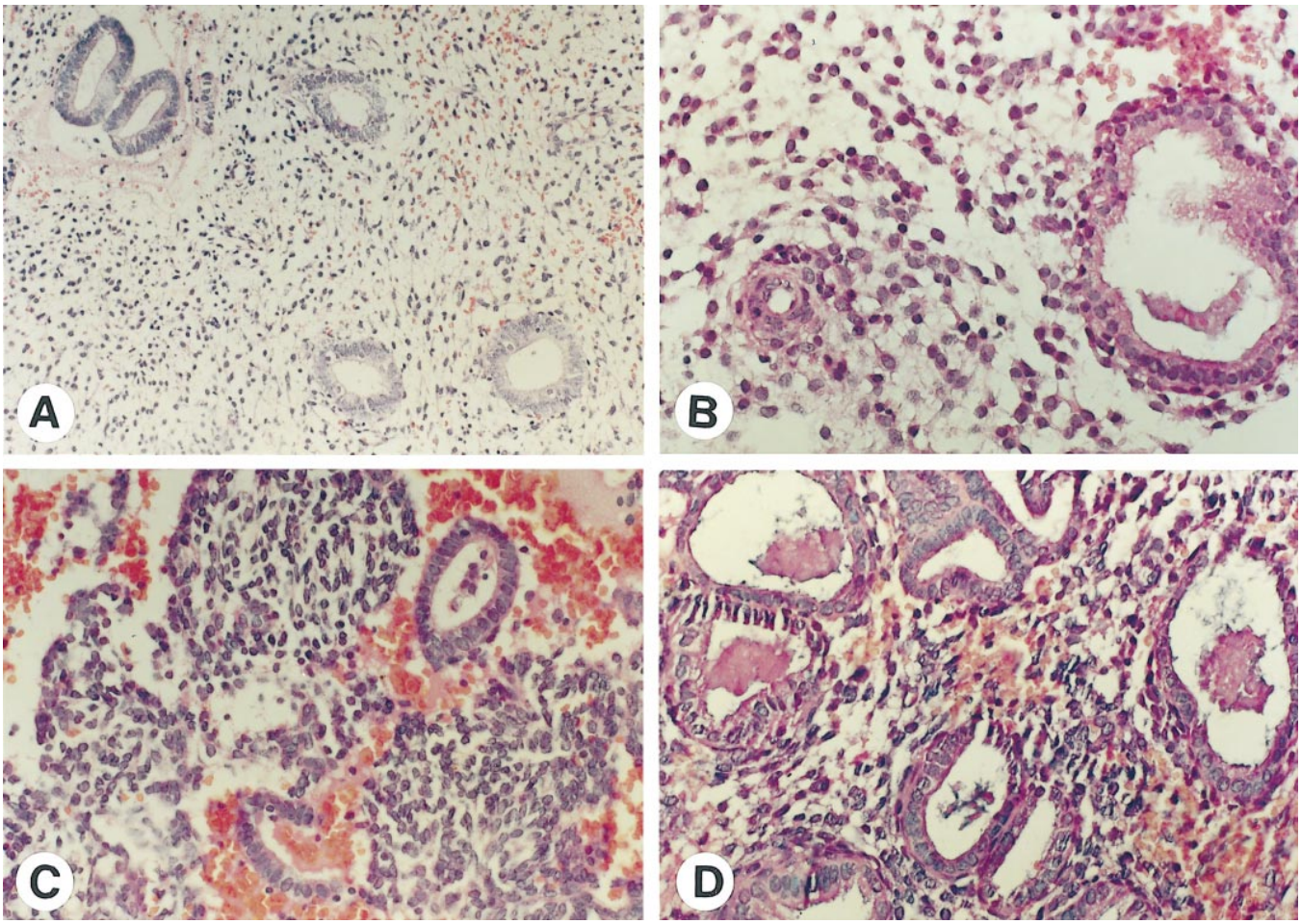


**Figure 4.** Histology of the endometrium in Uniplant users at different phases of their ovarian cycles. Original magnification: (**A**) ×200; (**B**), (**C**) and (**D**) ×400. (A) Women devoid of follicular development. (**B**) Women with a persistent non-luteinized follicle. (**C**) Women with breakthrough bleeding. (**D**) Ovulatory Uniplant users.

resembled day 24 in a spontaneous menstrual cycle. The secretion of the endometrial glands was prominent, associated with minimal stromal oedema (Figure 4D).

## Discussion

The prospective design of this study allowed the assessment of ovarian function every other day, in the same subject, during the study period. Clinical, ultrasound, hormonal and histological findings suggested the operation of different mechanisms of pregnancy prevention during the 1 year of use of the nomegestrol acetate subdermal implant. The assessment of ovarian function indicated that anovulation (75%) is the principal contraceptive mode of action, particularly in the first months after the implant insertion. Among the anovulatory cycles, the development of a persistent non-luteinized follicle (63%) was a more frequent finding than a lack of follicular development (12%).

It is interesting to note that subjects who were initially devoid of follicular maturation were able to initiate follicular growth or ovulate in subsequent months. This confirms that ovarian response to the progestin implant varies widely among individuals, and it is time and dose dependent (Lähteenmäki and Lähteenmäki, 1985). A similar finding has been reported by Brache *et al.* (1990) in Norplant users, where ovulation increased dramatically from less than 25% in the first year to 75% by the fifth year of use.

The diagnosis of persistent non-luteinized follicle was based on vaginal ultrasound images and the hormonal profile which indicated the absence of a LH and FSH surge when the diameter of the leading follicle had reached a size consistent with a pre-ovulatory follicle. The vaginal ultrasound scan demonstrated an absence of internal echoes in the leading follicle. After approximately 18–20 days the serum oestradiol and progesterone concentrations remained persistently low. It is interesting to note that oestradiol secretion in persistent non-luteinized follicle was time dependent. Follicular diameter and oestradiol secretion had a high degree of linear correlation for 18–20 days; thereafter, oestradiol secretion decreased, allowing the possible initiation of another wave of folliculogenesis in spite of the presence of enlarged inactive follicle. Our data do not explain the mechanism responsible for a lack of gonadotrophin release in cases of persistent follicle. A direct effect of the progestogen on the pituitary, reducing the periovulatory hypersensitivity to gonadotrophin-releasing hormone (GnRH) and oestradiol, has been postulated as the cause of the absence of LH release in these subjects (Devoto *et al.*, 1995; Barnhart *et al.*, 1997).

However, in addition, recent investigations have highlighted that sex steroids alone do not seem to be sufficient to stimulate the normal mid-cycle LH surge (Taylor *et al.*, 1995). Inhibin has recently been postulated as a modulator of the LH peak (Taylor *et al.*, 1995). Our data support the notion that progestin causes a disorderly pattern of folliculogenesis but it is possible that changes in secretion of inhibin and other peptides could contribute to development of persistent non-luteinized follicle in Uniplant users. A direct effect of this synthetic progestin upon granulosa cell physiology cannot be excluded as the cause of anovulation in these subjects as well (Chandrasekher *et al.*, 1991).

In this investigation the ovulation process was noted to be present after 6 months of Uniplant insertion. Eight subjects underwent ovulation, representing a total of 25% of the cycles in our series. It is interesting that the AC of progesterone in spontaneous cycles was significantly higher compared with the AC of luteal progesterone in Uniplant ovulatory cycles ($P < 0.05$), suggesting an inadequate luteal phase in these subjects. A similar finding was reported by Shaaban *et al.* (1993) in Norplant users, suggesting inadequate luteal phase to be a common mechanism preventing conception in progestogen-only contraceptive subdermal implants if ovulation occurs.

The endometrial changes reported confirm the varied effects of the progestin on the endometrium (McConn and Rotter, 1994). In Uniplant users who became amenorrhoeic, the histological assessment of the endometrium showed inactive epithelium consistent with the absence of follicular maturation and lack of oestradiol secretion. Endometrial changes such as glands with inactive epithelium, absence of mitosis, irregular formed gland in close proximity to large venous vessels, poor development of arterioles and oedema of the stroma are the principal feature of the endometrium in Uniplant users. These endometrial changes may contribute to the prevention of pregnancy in Uniplant users.

Implantation is a complex process, and success depends on a large number of interacting variables such as endometrial gland morphometry and volume (Rogers *et al.*, 1991, 1996) and endometrial proteins such as integrins (Lessey *et al.*, 1994). The endometrial changes induced by the synthetic progestin disrupt the endometrial morphology, which may lead to prevention of pregnancy by altering the molecular factors involved in human implantation. However, no obligatory markers of human uterine receptivity have yet been identified.

In conclusion, these findings suggest that inadequate follicular growth, anovulation, inadequate luteal phase, disruption of the endometrial architecture and, in particular, the development of persistent non-luteinized follicles, are the principal mechanisms of contraceptive action of the nomegestrol acetate subdermal implant.

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