Original research article

Effects of a single Silastic® contraceptive implant containing nomegestrol acetate (Uniplant) on endometrial morphology and ovarian function for 1 year☆

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Abstract

Purpose: This study was undertaken to evaluate the effects of a subdermal implant containing nomegestrol acetate (Uniplant) on endometrial histology and ovarian function.

Methods: Twenty healthy female volunteers of reproductive age were included and completed a menstrual diary throughout the study. Hysteroscopy, transvaginal sonography and blood sampling were performed prior to implant insertion (control cycle) and following 6 and 12 months of Uniplant use. Transvaginal sonography was performed every other day from Day 8 of the cycle up to the obtainment of sonographic evidence of a 12-mm follicle, then every day until the obtainment of sonographic evidence of follicular rupture and thereafter every other day until the next menstrual bleeding. Blood samples were taken for the measurement of estradiol, follicle-stimulating hormone, luteinizing hormone and progesterone on the same days on which transvaginal sonography was performed. The implants were removed after 1 year.

Results: Twenty percent of cycles were ovulatory, and 80% were anovulatory. The development of persistent nonluteinized follicle occurred in 40% of all cycles studied, inadequate luteal phase occurred in 20% of cycles and no follicular development occurred in 40%. Endometrial thickness remained below 8 mm in all cycles studied. Alterations in endometrial vascularization were observed in all treated cycles.

Conclusion: Our results suggest that this long-acting contraceptive method affects follicular growth and endometrial vascularization, disrupts endometrial architecture and leads to inadequate luteal phase.

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1. Introduction

Irregular menstrual patterns are an inevitable side effect of long-acting progestogen-only contraceptive methods [1]. Bleeding disorders may range from amenorrhea, to irregular and unpredictable spotting or light bleeding [2] to episodes of prolonged and frequent bleeding or spotting [3,4]. Heavy bleeding is rare, although prolonged episodes of light bleeding may occasionally add up to a greater volume of total blood loss per month than what the woman may have experienced in her normal menstrual cycles [5]. The mechanisms underlying these disturbances are still poorly understood, and further studies are required in order to improve the treatment or prevention of unpredictable bleeding.

Uniplant is a long-acting subdermal implant containing 55 mg of nomegestrol acetate that offers contraceptive efficacy for 1 year [6]. The exact mechanism of action of this implant is not completely understood, although previous studies have demonstrated that its principal contraceptive mechanisms include alterations in cervical mucus, ovarian function and endometrial thickness [7,8].

Although Uniplant leads to a reduced number of bleeding days per cycle in some women, some users of this contraceptive implant experience intermenstrual and irregular bleeding. Studies of biopsied tissue have provided limited information on the appearance and function of

endometrial vessels in vivo; however, direct hysteroscopic inspection would provide more specific data on superficial vascular changes related to irregular bleeding during the use of progestogens. To study the mechanism of action of Uniplant, hysteroscopy and endometrial histology were performed, and endocrine and sonographic evaluations of follicular function were carried out prior to implant insertion (control cycle) and at 6 and 12 months of Uniplant use.

2. Materials and methods

Following Institutional Review Board approval, 20 healthy female volunteers with no history of gynecological or endocrine disorders were enrolled in this study at the Maternidade Climério de Oliveira, the maternity teaching hospital of the Federal University of Bahia (Salvador, Bahia, Brazil). All subjects gave their informed consent. None of the participants had used hormonal contraception during the 6 months prior to recruitment. Procedures for the manufacture, insertion and removal of this implant were carried out as previously described [6]. The implants were removed after 1 year of use.

Venous blood samples were drawn every other day from Day 8 of the cycle up to the obtainment of sonographic evidence of a 12-mm follicle, then every day until the obtainment of sonographic evidence of follicular rupture and thereafter every other day until the next menstrual bleeding. Blood sampling was carried out prior to implant insertion (control cycle) and following 6 and 12 months of Uniplant use. Blood was collected into heparinized vials, and plasma was recovered after centrifugation and kept frozen at $-20°C$ until analyzed.

2.1. Hormone measurements

Progesterone (P) was determined by radioimmunoassay (RIA) using commercially available kits (Diagnostic Products Corporation, Los Angeles, CA, USA). The sensitivity was 0.02 ng/mL (0.09 nmol/L), and the interassay correlation coefficient of variation (CV) was 6.4%. The normal values are 0.09–28 ng/mL (0.3–89 nmol/L). According to this method, ovulation occurred when P plasma levels reached 3.0–28.0 ng/mL (9.0–89 nmol/L).

Estradiol (E_2) was determined by RIA using a commercial kit from Diagnostic Products Corporation. The sensitivity was 0.28 pg/mL (5.3 pmol/L), and the interassay CV was 5.5%. The normal values are 38–400 pg/mL (146–1468 pmol/L).

Luteinizing hormone (LH) was analyzed by RIA using a commercial kit from Diagnostic Products Corporation. The sensitivity was 1.21 IU/L (conversion factor to International System of Units, 1.00), and the interassay CV was 8.3%. The normal values for this method are 15–90 IU/L.

Follicle-stimulating hormone (FSH) was analyzed by RIA using a commercial kit from Diagnostic Products Corporation. The sensitivity was 0.7 IU/L (conversion factor to International System of Units, 1.00), and the interassay CV was 5.6%. The normal values of this method are 5.9–16.4 IU/L.

2.2. Hysteroscopy

Outpatient hysteroscopy was performed using a 4-mm diagnostic hysteroscope (Storz, Tuttiligen, Germany). The procedure was performed under local anesthesia using 5 mL of 1% lidocaine at the junction of the cervical and vaginal mucosae near the points of insertion of the uterosacral ligament. Uterine distention was obtained by infusing 0.9% saline at a constant flow at an average pressure of 120 mmHg, as controlled by a hysteromat (Storz). The use of the 4-mm hysteroscope does not require cervical dilatation, and the level of pain endured by the patient during the procedure is, therefore, greatly minimized. Upon the introduction of the hysteroscope, the uterine cavity was visualized and the endometrial vasculature was observed. The presence of any intrauterine pathology that could account for bleeding was noted. When the procedure was terminated, a 4-mm Karman curette was introduced into the uterine cavity. The curette was attached to a 10-mL syringe to produce vacuum, and the endometrium was aspirated. The material was fixed in 0.4% formalin and sent to pathology. Hysteroscopy was performed in all subjects during the control cycle (prior to insertion), in 10 women at 6 months and in 9 women at 12 months following Uniplant insertion.

2.3. Follicular development

Follicular growth pattern was assessed in all subjects using transvaginal sonography to examine both ovaries, as described by Osmers [9] and Goswamy [10]. Scans were initiated on Day 8 of the cycle and were performed on each day on which a blood sample was taken, as described above. Follicular rupture was diagnosed when an echo-negative structure disappeared or when its diameter decreased by >50%. In those subjects who had prolonged cycles or who developed amenorrhea, transvaginal sonography was performed thrice a week for at least 60 days. Endometrial thickness was measured from the proximal to the distal echogenic interface of the junction between the endometrium and the myometrium by an electronic caliper built into the machine. Only the longitudinal section of the uterus was used for the measurement of uterine and endometrial thicknesses. To evaluate the ultrasonographic texture of the endometrium, the following parameters were used: (a) a central linear echo representing the endometrial cavity that is often surrounded by two linear echoes representing the myometrial junctions; (b) hypoechogenic layers surrounding the central linear echo representing the growing endometrium; and (c) an increasing echogenicity starting from the peripheral borders of the myometrial–endometrial echoes representing differential changes of endometrial layers. The diagnosis of a persistent nonluteinized follicle was based on the absence of internal echoes in the leading follicle, as confirmed by transvaginal sonography and a hormone profile in which no FSH or LH surge was detected when
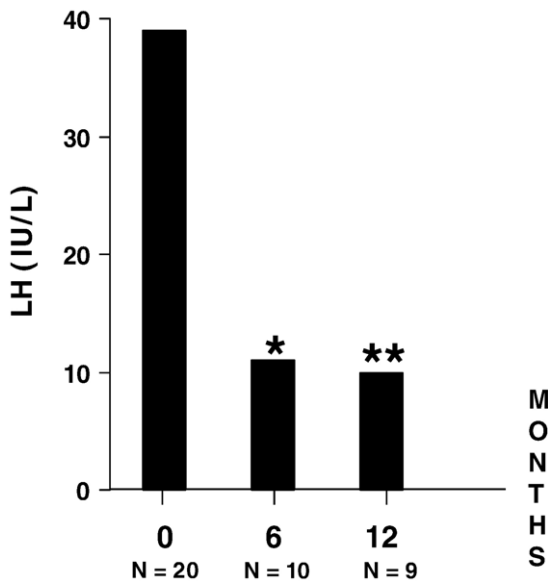
Fig. 1. Levels of LH during the control cycle and during 12 months of Uniplant use. *p<.05, **p<.01 (mean±SE).

the diameter of the leading follicle had reached a size consistent with a preovulatory follicle. After approximately 18–20 days, serum E_2 and P concentrations remained persistently low. The diagnosis of inadequate luteal function was made when transvaginal sonography indicated a leading follicle with a diameter larger than that of control subjects and when the hormone profile indicated a decrease in FSH and LH surges at the moment when the diameter of the leading follicle had reached a size consistent with a preovulatory follicle. After approximately 18–20 days, serum E_2 and P concentrations remained persistently lower than those found in control subjects.

2.4. Cervical cytology

Cervical cytology was performed before and after 1 year of Uniplant use.

3. Results

The characteristics of the patients on admission were as follows: age (mean±SE), 24±1.8 years (range, 18–35 years); weight (mean±SE), 54.6±2.8 kg (range, 40–71 kg); parity,

Table 1
Characteristics of each cycle studied

	6th month (n=10)	12th month (n=9)
P>5.0 ng/L (≥16.0 nmol/L)	1	3
Mean E_2>control (not significant)	4	5
Mean LH lower than that of controls	10	9
Follicular growth and rupture; luteal activity	2	2
Persistent nonluteinized follicle; no luteal activity	4	5
No follicular growth; no luteal activity	4	3

One subject moved to another state very far from Bahia on the third month of Uniplant use.

Fig. 2. Hysteroscopic view of superficial endometrial vessels. Small surface petechiae in a Uniplant user on Day 24 of the menstrual cycle.

1.2 (range 0–3); systolic blood pressure (mean±SE), 15.33±0.23 kPa (range, 13.3–16.0 kPa) [115±1.7 mmHg (range, 100–120 mmHg)]; diastolic blood pressure (mean± SE), 9.9±0.19 kPa (range, 8.0±10.4 kPa) [74±1.4 mmHg (range, 60–78 mmHg)].

All pretreatment cycles were ovulatory according to P, E_2, FSH and LH measurements, endometrial thickness and follicular growth and rupture. The measurements carried out over a 12-month period showed no statistically significant differences in plasma concentrations of E_2, while LH levels were significantly lower than those during the control cycle. The mean maximum preovulatory E_2 peak was 486.0±57.4 pmol/L (mean±SE) during the control cycle, 450.1±60.3 at 6 months and 472.4±48.9 at 12 months of implant use, respectively. The mean LH peak during the control cycle was 37.0±4.8 IU/L (mean±SE), decreasing to 13.9±1.7 and 12.4±1.2 at 6 and 12 months of Uniplant use, respectively (p<.01 when compared to control) (Fig. 1).

Fig. 3. Hysteroscopic view of superficial endometrial vessels. Small surface petechiae in a Uniplant user on Day 14 of the menstrual cycle.

According to P levels, 80% of treated cycles studied were anovulatory. Ovulation occurred when P plasma levels reached 9.0–89 nmol/L. The mean maximum P peak decreased from 36.7 ± 3.9 nmol/L during the control cycle to 26.1 ± 2.8 and 25.8 ± 3.1 at 6 and 12 months of treatment, respectively ($p < .05$ when compared to control). According to transvaginal sonography, three different patterns of follicular development were seen: follicular growth and rupture, persistent nonluteinized follicle and no follicular growth (Table 1). Follicular growth and rupture were observed in 20% of treated cycles, while the presence of persistent nonluteinized follicles was observed in 40% of treated cycles. All persistent nonluteinized follicles disappeared spontaneously within a maximum of 60 days. In 40% of the cycles studied, no follicular development was observed. On average, these proportions were similar at both 6 and 12 months of Uniplant use.

Endometrial thickness remained below 8 mm during 12 months of Uniplant use, even during ovulatory cycles (20% of all cycles studied).

Hysteroscopy revealed an increase in the number of endometrial vessels in all treated cycles compared to the control cycle during both the follicular and luteal phases of the cycle (Figs. 2 and 3); this increase, however, was not observed in amenorrheic women.

The endometrial histology of those Uniplant users in whom no follicular activity was detected showed endometrial stroma with sparse lymphocytic infiltration and cuboidal epithelial cells. Uniplant users with persistent nonluteinized follicles showed tortuous endometrial glands, spiral arterioles and deciduoid cells with glandular secretion (Fig. 4). In ovulatory Uniplant users, an endometrial biopsy was taken on Day 24 of the menstrual cycle; however, endometrial dating was indicative of Day 20 of the menstrual cycle. Histological endometrial findings in these women demonstrated tortuous endometrial glands with glandular secretion. The stroma showed minimal edema and few vessels with periarteriolar stroma cuffing. There
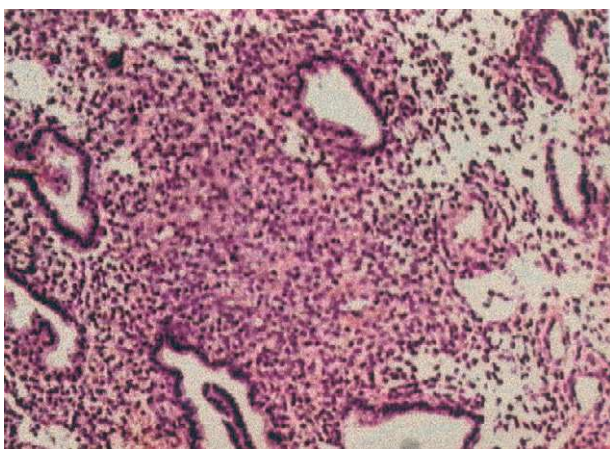

Fig. 4. Histology of the endometrium in a Uniplant user on Day 24 of the menstrual cycle. Spiral arterioles and deciduoid stromal cells are seen. Original magnification, ×200.

was insufficient material for analysis in three women in Cycle 6 and in two women in Cycle 12. No significant differences were observed between Cycles 6 and 12. No correlation was observed between histological features and bleeding patterns.

3.1. Bleeding patterns during 12 months of Uniplant use

A normal menstrual cycle (26–32 days) occurred in 11 women. Six women experienced one or two episodes of amenorrhea, which ranged from 90 to 134 days in duration, while two women experienced three episodes of intermenstrual bleeding (4–6 days) during 12 months of Uniplant use. One woman had two episodes of prolonged bleeding (16–20 days).

4. Discussion

Nomegestrol acetate is a 19-nor-P derivative with potent progestational activity and no androgenic or metabolic side effects [11–13]. Nomegestrol acetate, given orally at doses of 1.25, 2.5 and 5.0 mg/day, exerts a potent antiovulatory effect that probably acts at the hypothalamic–pituitary levels and also on the ovary [14,15]. In this study, 55 mg of nomegestrol acetate was used in a single Silastic® implant, which has been shown to provide a very stable release throughout the duration of use.

Twenty healthy women with normal menstrual cycle were recruited for this study. Results showed that nomegestrol acetate blocked ovulation in 80% of the cycles studied for 1 year. Nomegestrol acetate also exerted effects on ovarian function, consisting of disturbances in follicular growth and rupture, and lower plasma levels of P. Levels of LH and FSH were also significantly lower than those of controls, probably indicating an effect at the hypothalamic–pituitary level.

The presence of elevated levels of E_2 and the absence of a gonadotropin surge during the follicular phase indicate that the positive feedback of E_2 on gonadotropins is disrupted. This mechanism has previously been reported in studies on ST-1435 nesterone and other progestogens [16–18]. Our findings of elevated E_2 levels and the absence of LH surge in the great majority of cycles are in accordance with these results. Folliculogenesis inhibition is associated with a decrease in LH and FSH ratio, which mainly depends on the pulse frequency of LH-releasing hormone [19]. In our study, the LH and FSH ratio was >2:1 in 47.7% of the cycles studied. These results may be explained by the follicular activity observed by ultrasonography in the majority (60%) of the cycles studied for 1 year. Follicular development and rupture were observed in 20% of the cycles studied in Uniplant users. This study shows that a single Silastic® capsule of nomegestrol acetate exerts an antiovulatory effect in women.

Disturbances in follicular growth and rupture, such as no follicular growth or rupture and persistent nonluteinized follicles, were observed. All persistent nonluteinized follicles

disappeared spontaneously within 60 days. Disturbances in follicular growth and rupture have also been reported in previous studies on levonorgestrel implants and levonorgestrel-releasing IUDs [20–23].

Cervical cytology was performed before and after 1 year of Uniplant use; no changes were observed. The mean peak levels of P, LH and FSH were lower during ovulatory cycles than during the control cycle. This may explain the contraceptive effect of Uniplant even when ovulation occurs. Endometrial thickness in treated cycles was below 8.0 mm in all women throughout the study, even in cycles in which high E_2 levels were recorded. This may be due to a direct effect of nomegestrol acetate on the endometrium. Bakos et al. [24] found that only one thin echogenic line was seen from menstruation to Day 7. From Days −6 to −1, a change from one to three thin lines, together with an increasing hypoechogenic texture between the lines, was observed. These changes corresponded to the increasing serum concentration of E_2 and to increasing endometrial thickness. Changes in endometrial surface appearances and small surface vessels were assessed by hysteroscopic observation. Surface vascularization was defined as the area of endometrial surface covered by relatively distended small vessels. The area of obvious vascularization was greater in Uniplant users than in controls. The number of irregular vascular patterns increased with the duration of exposure to Uniplant, and these observations are in accordance with data from previous studies with Norplant [25].

Disturbances in endometrial histology were observed in all cycles studied and included: insufficient material, decidualized stroma, atrophy, inflammatory cell infiltration and glandular dilatation. These endometrial changes may contribute to the contraceptive efficacy of Uniplant. The histological endometrial changes reported in this study confirm the varied effects of this progestin on the endometrium [26,27].

In conclusion, Uniplant has several contraceptive mechanisms. The first mechanism involves a suppressive effect on follicular development that causes anovulation in the majority of women. A second mechanism involves disturbances in follicular growth and rupture, such as persistent nonluteinized follicles. The third mechanism involves suppression of endometrial growth as seen by transvaginal sonography, which accounts for the reduction in menstrual blood loss and, in some cases, amenorrhea. The mechanism involving the histological endometrial changes mentioned above may contribute to the contraceptive effect of Uniplant. The mechanisms underlying these disturbances are still poorly understood; a better understanding of these mechanisms should help in the development of techniques to treat or prevent unpredictable bleeding.

In summary, the results of this study show that Uniplant is a long-acting contraceptive method that probably acts at the hypothalamic–pituitary level but also exerts an effect on the ovary and the endometrium. These properties suggest the use of Uniplant as a contraceptive agent.

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