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Ultrasonographic features of the endometrium and the ovaries in women on etonogestrel implant

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ABSTRACT

Objective *To evaluate the ultrasound features of the endometrium and ovaries in women on etonogestrel implant, and to correlate these features with the bleeding pattern.*

Methods *Observational study including 188 consecutive women presenting for follow-up transvaginal ultrasound examination after insertion of an etonogestrel implant contraceptive device. Thirty women had more than one follow-up examination. The bleeding pattern was considered abnormal if, in the last 3 months, there were more than five episodes of vaginal bleeding, or there was prolonged bleeding exceeding 14 consecutive days.*

Results *At first follow-up examination, the mean age was 29.7 years and 47% of women had an abnormal bleeding pattern. Most bleeding episodes were of less intensity than menses. The mean endometrial thickness (ET) on ultrasound was 2.9 mm (standard deviation, 2.0). Ovarian follicle growth exceeding 5 mm was observed in 60% of the cases. Ovulation was demonstrated in one woman. Univariate analysis showed a positive association (*$P < 0.01$*) between ET, bleeding pattern, and bleeding intensity. Follicle growth was positively associated (*$P < 0.01$*) with ET, bleeding pattern, and interval between insertion and examination. Multivariate analysis showed that the ET was on average 1.25 mm greater in women with abnormal bleeding (*$P = 0.0001$*). The odds of finding follicle growth were 2.8 times higher (95% confidence interval, 1.2–6.2) in women presenting with a three-layer type of endometrial morphology. There was no association between the other patients' characteristics and the bleeding pattern.*

Conclusions *Abnormal uterine bleeding in women on etonogestrel implant was associated with follicle growth and a thicker, three-layer type of endometrium, suggesting incomplete ovarian inhibition and estrogen stimulation of the endometrium.*

INTRODUCTION

The etonogestrel implant (Implanon®, NV Organon International, Oss, The Netherlands) is a long acting subdermal single rod contraceptive implant containing the progestative etonogestrel. It is inserted under local anesthesia in the medial side of the upper arm. The progestative agent is released in a continuous way during at least 3 years. The contraceptive effect is reported to be due to complete ovulation inhibition, but also to endometrial atrophy and to thickening of the mucus in the cervical canal[1–4]. Abnormal uterine bleeding is the major adverse effect of the method. The aim of the present study was to evaluate the ultrasound features of the endometrium and of the ovaries in women on etonogestrel implant, and to correlate these findings as well as the patients' characteristics with the bleeding pattern.

PATIENTS AND METHODS

This study included all consecutive women presenting for follow-up after the insertion of an etonogestrel implant contraceptive rod between 21 February 2000 and 20 December 2001. Exclusion criteria were as follows: insertion for less than 4 weeks, the concomitant use of hormonal therapy, and the diagnosis of menopause. Oral informed consent was obtained beforehand. Patients' history included patients' age, weight, height, parity, gravidity, and date of etonogestrel implant insertion. The vaginal bleeding pattern in the previous 3-month interval (or the bleeding pattern since insertion in the seven patients with an interval between 1 and 3 months) was recorded as either amenorrhea (no bleeding or spotting); infrequent bleeding (one or two episodes of bleeding/spotting); normal bleeding (three or four episodes); frequent bleeding (five or more episodes); prolonged bleeding (bleeding/spotting episodes exceeding 14 days' duration); or postpartum (history of delivery or miscarriage within the last 3 months). For most of the analysis two subgroups were considered: the 'normal'

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bleeding subgroup, including women with amenorrhea, infrequent, or normal bleeding, vs. the 'abnormal' bleeding subgroup, including women with frequent or prolonged bleeding. The bleeding intensity was quantified as either spotting (described as less heavy than menses) or as bleeding with at least the same intensity as menstrual flow.

Transvaginal ultrasound examination was performed to evaluate the endometrium and ovarian follicle growth. The endometrium was measured as total thickness in the sagittal plane. The echolucent layer surrounding the endometrium was not included. In the presence of intracavitary fluid, both single layers were measured and the sum was recorded. The recorded sonographic features of the endometrium included the presence or absence of a three-layer pattern, as seen in the follicular phase of a spontaneous menstrual cycle; the regularity of the outline; the sonographic evidence of a polyp (recorded as absent, present, or possibly present); the presence or absence of intracavitary fluid. The ovaries were evaluated, and the presence of follicle growth was documented. A follicle was defined as a regular thin-walled unilocular sonolucent cystic structure within the ovary. The maximal diameter of the largest follicle and the number of follicles exceeding 5 mm in diameter were recorded. If the follicle was oval in shape, the average of three diameters in two perpendicular cross-sections was calculated.

Patient characteristics, bleeding pattern, and ultrasonographic features were analyzed and compared. SAS, S-Plus, and Matlab were used for statistical analyses. These included linear mixed effects models, linear and logistic regression, stepwise selection procedure, and Least Squares Support Vector Machines, which is an intrinsically non-linear model[5,6].

RESULTS

The dataset included 224 ultrasound evaluations in 188 women (Table 1). Thirty of them had more than one follow-up examination; two women had three ultrasound evaluations, and two women underwent four scans. The first part of the analysis involved only the cross-sectional data at the first ultrasound examination (188 examinations). The mean age was 29.7 years (standard deviation (SD), 6.6; range, 16–49), with an average parity of 1.2 (SD, 1; range, 0–5) and a mean body mass index of 23.6 (SD, 4.3; range, 16.1–40.8). The interval between the insertion of the etonogestrel implant and the ultrasound examination ranged from 1 to 20 months (mean, 4.1; SD, 2.8). Fifty-three percent of women reported a 'normal' bleeding pattern (including amenorrhea, infrequent bleeding, and normal bleeding), whereas 47% had an 'abnormal' bleeding pattern (frequent or prolonged bleeding). The majority (67.2%) of women with vaginal bleeding reported a bleeding intensity that was less than habitual menstruation. The mean endometrial thickness on ultrasound scan was 2.9 mm (SD, 2.0; range, 0–13.5). The endometrium was found to have a regular outline in the vast majority of cases (95%), and in 22.2% of cases a three-layer pattern was reported. Polyps were diagnosed in five women (2.7%). Ovarian follicles exceeding 5 mm were seen in 60.6% of cases. In one patient, 16 months after insertion, one ovary had a sonographic appearance of a corpus luteum. Progesterone measurement confirmed a luteal level (4.4 ng/mL). Two other women showed ovarian enlargement not due to follicle growth: one woman showed ultrasound features of a dermoid, and the other of an endometrioma.

Table 1 Patients' characteristics at first visit: $n = 188$

	Mean	*Median*	*Range*	*SD*
Age (years)	29.7	29	16–49	6.6
Weight (kg)	64.7	62	46–111	12.7
Height (cm)	165.3	165	145–187	6.3
BMI (kg/m^2)	23.6	22.7	16.1–40.8	4.3
Interval (months)	4.1	3	1–20	2.8
Parity	1.2	1	0–5	1.1
Gravidity	1.3	1	0–5	1.2
Endometrial thickness (mm)	2.9	2.5	0–13.5	2.0

BMI, body mass index; 'interval' is defined as the time elapsed between insertion of the etonogestrel implant and the first ultrasound examination; the endometrial thickness was measured on transvaginal ultrasound scan and included the total (double layer) thickness in the sagittal plane.

Univariate analyses showed that endometrial thickness was significantly associated with the bleeding pattern and intensity (Table 2). The mean endometrial thickness was 2.5 mm in women with a normal bleeding pattern vs. 3.6 mm in those presenting with abnormal bleeding ($P < 0.01$) (Figure 1). In women with amenorrhea the average endometrial thickness measured 2.1 mm vs. 2.8 mm in those with spotting ($P < 0.01$) and 4.1 mm in women reporting bleeding of at least the intensity of menstruation ($P < 0.01$). There was a borderline positive association between the sonographic echogenicity (presence of a three-layer pattern) and the interval between insertion and ultrasound examination ($P = 0.08$). The thicker the endometrium, the more likely there was to be a three-layer pattern on ultrasound scan ($P = 0.02$). There was a positive correlation between the maximal ovarian follicle diameter and the interval between insertion and ultrasound examination ($r = 0.28$; $P < 0.01$). The larger the maximal follicle, the thicker the endometrium (endometrial thickness increases by 0.04 mm for each 1 mm increase in follicle diameter; $P < 0.01$), the more likely the woman experienced an abnormal bleeding pattern (for each 1-mm increase in follicle diameter, the risk for an abnormal bleeding pattern increases by 4%; $P < 0.01$), and the greater the chance of finding a three-layer pattern (for each 1-mm increase in follicle diameter, the likelihood of there being a three-layer pattern increases by 3%; $P = 0.06$). There was a negative association between the occurrence of an abnormal bleeding pattern and the interval between insertion and ultrasound examination (odds ratio, 0.88; $P = 0.03$). The women reporting fewer than five bleeding episodes in a 3-month interval complained less frequently of heavy bleeding (odds ratio, 0.59; 95% confidence interval, 0.42–0.82) and had a thinner endometrium (−1.32 mm; $P < 0.01$). Women reporting bleeding episodes of at least the intensity of menses had a thicker endometrium on ultrasound ($P < 0.01$). There was no association between the other patient characteristics and the bleeding pattern.

The ultrasound features were analyzed against the other variables using multivariate analysis with stepwise selective models. Non-linear associations between the response and the

Table 2 Univariate analysis (*P*-values)

	Endometrial thickness	*Echogenicity*	*Follicle growth*	*Bleeding pattern*	*Bleeding intensity*
Age	0.23	0.20	0.18	0.67	0.81
Weight	0.18	0.39	0.14	0.40	0.40
Height	0.34	0.06	0.97	0.65	0.58
BMI	0.34	0.10	0.22	0.31	0.22
Interval	0.42	0.08	< 0.01	0.03	0.08
Parity	0.21	0.42	0.99	0.31	0.24
Gravidity	0.08	0.34	0.87	0.19	0.09
Bleeding pattern	< 0.01	0.17	< 0.01	—	< 0.01
Bleeding intensity	< 0.01	0.41	0.54	< 0.01	—
Endometrial thickness	—	0.02	< 0.01	< 0.01	< 0.01
Follicle growth	< 0.01	0.06	—	0.01	0.60

'Interval' is defined as the time elapsed between insertion of the etonogestrel implant and the first ultrasound examination. The endometrial thickness was measured on transvaginal ultrasound scan and included the total (double layer) thickness in the sagittal plane. Echogenicity stands for the presence or absence of a three-layer pattern of the endometrium. Follicle growth denotes the diameter of the largest follicle. Bleeding pattern: 'abnormal' bleeding is defined as five or more episodes over the last 3 months or episodes exceeding 14 days. Bleeding intensity was quantified as either 'spotting' (described as less heavy than menses) or bleeding with at least the same intensity as menstrual flow.

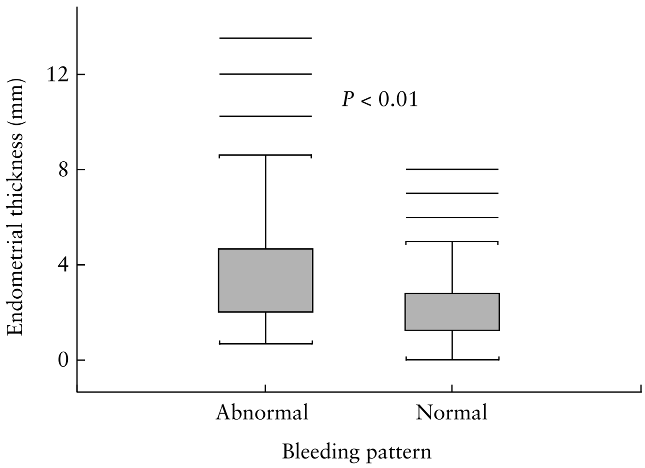

Figure 1 Endometrial thickness vs. bleeding pattern ('abnormal' bleeding pattern including 'frequent' and 'prolonged' bleeding).

Table 3 Prospective analysis using linear mixed models in the 30 women who underwent two vaginal ultrasound examinations (evolution of the variables between first and second scan)

Variable	*Scan 1*	*Scan 2*	P
Weight	mean 66 kg	mean 65 kg	0.89
BMI	mean 24	mean 24	0.91
Bleeding pattern	48% normal	37% normal	0.37
Bleeding intensity	75% 'spotting'	62% 'spotting'	0.32
Endometrial thickness	mean 2.9 mm	mean 2.4 mm	0.10
Follicle growth	mean 12.8 mm	mean 15.6 mm	0.44

BMI, body mass index. Bleeding pattern: 'abnormal' bleeding is defined as five or more episodes over the last 3 months or episodes exceeding 14 days. Bleeding intensity was quantified as either 'spotting' (described as less heavy than menses) or bleeding with at least the same intensity as menstrual flow. The endometrial thickness was measured on transvaginal ultrasound scan and included the total (double layer) thickness in the sagittal plane. Follicle growth denotes the diameter of the largest follicle.

explanatory variables were investigated by the use of Least Squares Support Vector Machines[5,6]. No significant difference between the performance of the intrinsically non-linear Least Squares Support Vector Machines model and the corresponding linear model with the same explanatory variables was detected. The endometrial thickness was on average 1.25 mm thinner in women with a normal bleeding pattern than in those with frequent or prolonged bleeding ($P = 0.0001$). If the amount of bleeding was reported to be at least as heavy as menses, the endometrial thickness was on average 1.15 mm thicker than in women with spotting or amenorrhea ($P = 0.0021$). The odds of finding follicle growth on ultrasound scan were 2.8 times higher (95% confidence interval, 1.2–6.2) in women presenting with a three-layer type of endometrium than in those with an echogenic endometrium.

The second part of the analysis was performed prospectively using linear mixed effects models and involved evaluation of the 30 women who underwent two or more scans, looking at the evolution of the variables between the first and second scans. There were no significant differences in any of the studied parameters, although there was a slight decreasing trend for endometrial thickness ($P = 0.10$) (Table 3).

DISCUSSION

The etonogestrel implant has direct effects on the endometrial progestin target sites and indirect effects by suppression of the hypothalamo–pituitary–ovarian axis[7] leading to ovulation inhibition. This results in an inactive or weakly proliferative endometrium[1,7–9]. Our findings confirm previous reports that the endometrial thickness on ultrasound scan does not usually exceed 4–5 mm[8]. Ovulation inhibition constitutes the main contraceptive effect of the etonogestrel implant[1–4] and is achieved within 1 day after insertion; it lasts for at least 3 years[2]. Follicle growth and estrogen synthesis remain present under etonogestrel implant. In a prospective series, Makarainen *et al.*[8] reported the first escape ovulation after 30 months following etonogestrel implant insertion. In our series an escape ovulation was detected 17 months after insertion.

Adverse effects of the etonogestrel implant are usually mild and include abnormal uterine bleeding, weight gain, acne, breast pain, and headache[8]. Previous studies reported a relatively high prevalence of frequent or prolonged bleeding in women on etonogestrel implant: Zheng *et al.*[10] reported a mean overall incidence of prolonged bleeding in 66.0% and 27.3% in the first and second years after insertion, respectively. In their series[10] the number of bleeding/spotting days per 90-day interval was 33.5 days in the first year vs. 19–21.5 days in the second year. The bleeding pattern under etonogestrel implant is reported to be unpredictable[11]. None of the patients' characteristics in our series had any predictive value as to bleeding pattern or intensity. It therefore seems impossible to select women, before insertion of etonogestrel implant, who are less likely to develop disturbing vaginal bleeding. All women ought to be properly informed before insertion about possible bleeding problems. Disturbed bleeding patterns are the most common adverse events[2,10,11] and are the major reason for premature removal of the implant. The discontinuation rates show striking geographic variation with figures as high as 30.2% in a European trial vs. 0.9% in a Southeast Asian study[11]. The reason for this wide range is unknown: the acceptability of spotting may differ from one woman to another.

The exact mechanism of progestin-induced breakthrough bleeding is incompletely understood. Varma and Mascarenhas[7] proposed that, besides changes in endometrial histology and thickness, progestins might modify endometrial vascular, angiogenic, steroid receptor and proto-oncogene function, causing uterine bleeding. Our data suggest that—at least a part of—the enhanced bleeding problems may be due to insufficient ovarian inhibition and to estrogen stimulation of the endometrium. Follicle growth was associated with a thicker, three-layer type of endometrium as seen in the follicular phase of a spontaneous menstrual cycle, although in spontaneous menstrual cycles the endometrial lining is usually thicker than in the study cases. Both follicle growth and follicular-phase-like endometrial changes were associated with more frequent and heavier vaginal bleeding.

There were some contradictory findings concerning the interval between insertion and transvaginal ultrasound examination: the longer the interval, the more likely follicle growth was found to be, but the less frequent bleeding problems were. Although these associations were weak and could not be confirmed in the multivariate analysis, this may suggest two different mechanisms for abnormal uterine bleeding in women on etonogestrel implant: one pathway could be by increased estrogen stimulation, and the other by progestogen-induced atrophy. The ultrasound evaluation may give a clue as to the possible therapy in women with abnormal bleeding: if estrogenic changes are seen, as demonstrated by the sonographic features of the ovaries and endometrium, a supplementary progestative may be considered. This hypothesis has to be tested in prospective trials.

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