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Ovarian function after seven years' use of a levonorgestrel IUD

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Abstract

Fifteen women with regular menstrual periods and seven amenorrheic women who had been using a levonorgestrel-releasing (LNg) IUD for more than seven years were studied. For controls, eight women using TCu380Ag IUDs for more than seven years were studied during two complete menstrual cycles. Ovarian function was assessed with hormonal determination and ultrasound examinations. The regularly menstruating women were studied for two complete menstrual cycles and the amenorrheic women for eight weeks.

In the regularly menstruating LNg-IUD users, according to progesterone levels, 93% of the cycles were ovulatory but just 58% of these 'ovulatory' cycles showed normal follicular growth and rupture. Follicular cysts and luteinization of regressing follicles were observed in 42% of the 26 'ovulatory' cycles studied.

SHBG capacity was decreased in the LNg-IUD users compared with the TCu380Ag users. Progesterone levels were lower in the LNg-IUD users compared with the TCu380Ag users but this difference was not statistically significant. Preovulatory estradiol and LH levels were lower in the LNg-IUD users than in the TCu380Ag users. These differences were not statistically significant.

For the amenorrheic women, five had follicular cysts that disappeared spontaneously within 45 days. Two women showed follicular development and rupture.

The presence of good cervical mucus was observed in 69% of the ovulatory cycles studied in the LNg-IUD users. This indicates that effects on cervical mucus cannot be the main mechanism of action of the LNg-IUDs.

It is concluded that LNg-IUDs may exert a contraceptive effect in many different ways, such as inhibition of ovulation, endometrial changes preventing implantation, alteration of physical and chemical properties of cervical mucus affecting sperm transport and subtle disturbances in hypothalamic pituitary ovarian function, resulting in alterations of follicular development and rupture.

Introduction

Levonorgestrel-releasing IUDs have been studied over a period of six years. Contraceptive efficacy has been reported to remain very high throughout the six-year period [1–3].

Previous studies on ovarian function in LNg-IUD users suggest that the majority of women studied had ovulatory cycles [4,5]. Nilsson et al. suggest that the amenorrhea that develops in many LNg-IUD users is caused by the local effect of the progestin on the endometrium [6]. The observation of Kurumäki et al. that in a group of women using levonorgestrel-releasing intracervical devices over a period of one year, none of the women developed amenorrhea [7], confirms Nilsson's observation.

Our previous study in LNg-IUD users in their fourth year of use demonstrated that, according to progesterone levels, 88% of the cycles studied were ovulatory. However, normal follicular growth and rupture was observed in only 53% of these cycles. Preovulatory estradiol, LH and mid-luteal progesterone levels were lower in LNg-IUD users compared with the controls [8].

The aim of the present study was to demonstrate the mechanism of action of the LNg-releasing IUD in women using this IUD for more than seven years, and also to verify the levonorgestrel levels in these women and the effects on SHBG capacity. Ovarian function was to be studied in detail by hormonal measurements, cervical mucus studies and ultrasonographic assessment.

Materials and methods

Twenty-two healthy volunteers using LNg-IUDs and eight volunteers using TCu380Ag IUDs, participating in a large field study on the clinical performance of these IUDs, were enrolled at their seven-year follow-up visit to the clinic. Seven of the LNg-IUD users had been amenorrheic for at least 6 months prior to the visit and fifteen had had bleeding at regular intervals. All subjects using TCu380Ag had regular menstrual cycles.

The cycle length in the TCu380Ag group was 26.8 ± 0.6 days (mean $\pm$ SE) and for the LNg-IUD group, it was 28.8 ± 1.4 days. This difference was not statistically significant. The age of the LNg-IUD users at the time of the study was 35.0 ± 1.4 years. The age of the TCu380Ag users was 34.2 ± 1.4 years (mean $\pm$ SE). This difference was not statistically significant.

The body weight of TCu380Ag and LNg-IUD users at the time of this study was 64.1 ± 2.1 kg and 61.3 ± 2.7 kg (mean $\pm$ SE), respectively. This difference was not statistically significant.

The LNg-IUDs were manufactured by Leiras Pharmaceuticals, Turku, Finland. The vertical arm of a plain Nova-T was coated with Silastic polymer impregnated with levonorgestrel and covered with silastic tubing (382 medical grade Elastomer, Dow Corning Corporation, Medical Products Division, Midland, MI, USA). The LNg-releasing IUD releases approximately 20 μg per 24 hours.

Venous blood samples were drawn every other day from day eight of the menstrual

cycle until sonographic evidence of a 12-mm follicle and then every day until sonographic evidence of follicular rupture, and thereafter every other day until the next menstrual bleeding. In the amenorrheic patients venous blood was drawn twice a week for 60 days. Blood was collected into heparinized vials and plasma was recovered after centrifugation and kept frozen at –20°C until analyzed.

Hormone determinations

Plasma concentrations of levonorgestrel were determined by a specific radioimmunoassay as described previously by Weiner and Johansson [9]. Both the antiserum and the tracer (15,16-^{3}H-d-norgestrel) with a specific activity of 30–50 Ci/nM were obtained from Schering AB, Berlin, Germany.

Extraction from plasma was performed with diethyl ether. Because of a small plasma blank, the practical detection limit was 25 pg. No correction was made for procedural losses, nor were the plasma blanks subtracted. The extraction recovery was 89–95%. With the extraction volume of 200 µl, the detection limit was 0.16 nmol/L. For random samples, the interassay coefficient of variation was 8.7% for samples < 1.0 nmol/L and 6.4% for those > 1.0 nmol/L. No cross-reactions were found between naturally occurring steroids and levonorgestrel.

SHBG capacity was determined using a time-resolved fluorimmunoassay kit from Pharmacia AB. The sensitivity was 0.8 nmol/L and the interassay coefficient of variation was 3.5%

Estradiol and progesterone were determined by radioimmunoassay using a commercial kit from Diagnostic Products Corporation, Los Angeles, CA, USA. The sensitivity was 29 pmol/L and 0.15 nmol/L and the interassay coefficient of variation was 5.3 and 7.2%, respectively.

FSH and LH were measured by radioimmunoassay using a commercial kit from Diagnostic Products Corporation, Los Angeles, CA, USA. The sensitivity was 1.2 IU/L and 2.0 IU/L and interassay coefficient of variation was 4.6 and 5.7%, respectively.

Follicular development

Follicular growth pattern was assessed in all volunteers by abdominal ultrasonography using a real-time sector scanner (ADR SL 4000) and employing the full bladder technique of Hackelöer et al. [10]. The examination started on day 8 of the cycle and was then performed every other day until sonographic evidence of a 12-mm follicle and then every day until sonographic evidence of a follicular rupture was obtained, and thereafter every other day until the next menstrual bleeding. Follicular rupture was diagnosed when the echo negative structure disappeared or decreased its diameter by more than 50%.

In the amenorrheic patients, abdominal ultrasonography was performed twice a week for 60 days. In the patients who developed follicular cysts, ultrasonography was performed three times a week until disappearance of the cysts. The patients who

showed small follicles or no follicular activity had ultrasonography performed three times a week until next menstrual bleeding.

Cervical mucus

Cervical mucus was collected from the endocervix using a 20-ml syringe and a polyethylene catheter. Cervical mucus was evaluated according to WHO criteria [11]. The maximum score for cervical mucus was 15. A score greater than 10 was indicative of good cervical mucus, favoring sperm penetration and a score of less than 10 represented unfavorable cervical mucus.

Cervical mucus was collected every other day from day 8 of the cycle until ultrasonographic evidence of a 12-mm follicle and then every day until evidence of ovulation. In the amenorrheic patients cervical mucus was collected twice a week for 60 days and in the patients with small follicles or follicular cysts, cervical mucus was collected every other day until onset of next menstrual bleeding.

Classification of ovarian function

Ovarian response was classified according to Landgren and Diczfaluzy [12] (Table 1).

Statistics

For statistical comparisons, Student's *t*-test for unpaired groups was used. Values are shown as mean $\pm$ SE.

Table 1

Reaction type	*Ovarian response*
A	No cyclic follicular activity No luteal activity
B	Cyclic follicular activity No luteal activity
C	Cyclic follicular activity Inadequate luteal activity
D	Ovulatory-like ovarian function

Results

Hormonal determinations

In the TCu380Ag group, 8 women and 15 cycles were studied. All cycles were ovulatory according to progesterone levels but 2 of them showed no follicular rupture.

In the levonorgestrel IUD group, 15 women with regular menstrual bleedings and 28 cycles were studied. According to estradiol and progesterone levels, 26/28 were ovulatory cycles and classified as type D according to Landgren and Diczfaluzy [12]. One cycle showed follicular activity but no luteal activity (type B), and the other cycle showed no follicular and no luteal activity (type A).

Seven women in the LNg-IUD group were amenorrheic. They were studied for 8 weeks. Six of them showed progesterone peaks above 15.0 nmol/L (type D) and one of them showed follicular activity and no luteal activity (type B).

The mean maximum LH peak for TCu380Ag users was 29.2 ± 4.5 IU/L (mean $\pm$ SE). For the LNg-IUD group with regular menstrual bleedings, cycles classified as type D had a mean maximum LH peak of 23.9 ± 5.1 IU/L. This difference was not statistically significant compared with TCu380Ag users.

The mean maximum progesterone peak for TCu380Ag users was 32.5 ± 3.2 nmol/L. For LNg-IUD users with type D cycles, it was 25.0 ± 1.7 nmol/L. This difference was not statistically significant compared with TCu380Ag users.

The mean maximum preovulatory estradiol peak for the TCu380Ag group was 806.6 ± 81.9 pmol/L. For the LNg-IUD group with type D cycles, it was 616.9 ± 80.8 pmol/L. This difference was not statistically significant compared with TCu380Ag users.

Ultrasound

In the TCu380Ag group, normal follicular growth and rupture was found in 13/15 cycles. In two cycles, follicular growth and no rupture was observed despite the high progesterone levels. These cycles were considered as luteinized unruptured follicle syndrome (LUF). The mean maximum follicular diameter for the TCu380Ag group was 20.5 ± 0.7 mm.

For the LNg-IUD users with type D cycles, 15/26 with normal follicular development and rupture were observed. The mean maximum follicular diameter was 20.9 ± 0.7 mm (Figure 1). This difference was not statistically significant compared with TCu380Ag users.

In 6/26 type D cycles in menstruating women, cyst development with mean maximum diameter of 34.9 ± 2.1 mm was observed (Figure 2). A follicular cyst was defined as a persistent follicle of >30 mm diameter.

Only small follicles (<15 mm), no rupture, no corpus luteum formation were observed in 5/26 cycles. All five cycles had progesterone levels above 15.0 nmol/L.

For the amenorrheic women, 5 women showed cyst formation above 30.0 mm (mean maximum diameter = 35.5 ± 1.7 mm). The cysts disappeared spontaneously within 45

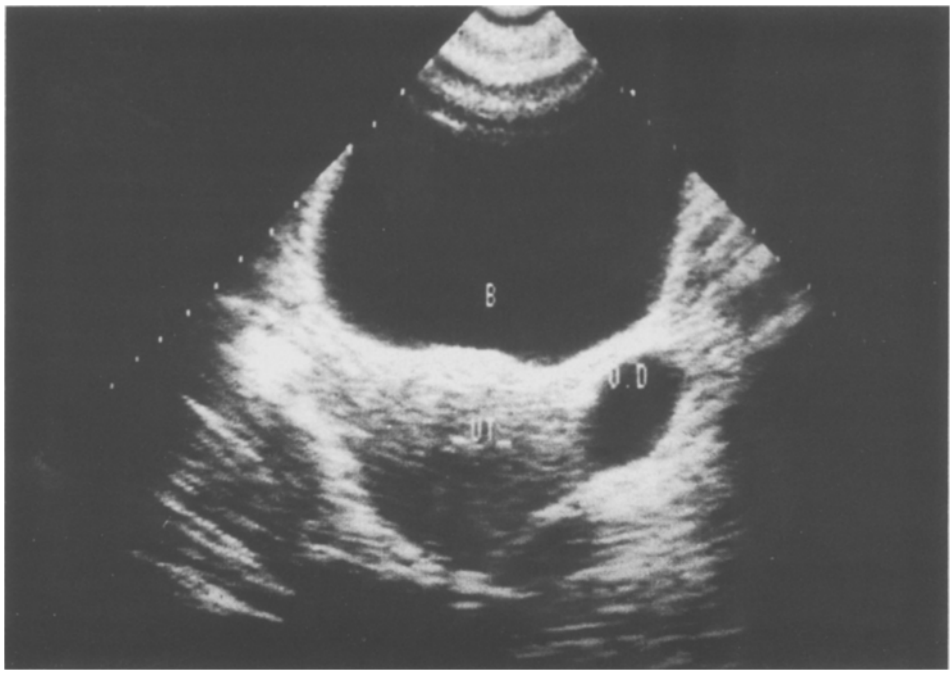

Figure 1. A typical ultrasound representation of a preovulatory follicle, which later ruptured. The woman had used a LNg-IUD for more than seven years. This picture was taken on day 15 of the cycle when LH level was 27.0 IU/L

days. Two women showed follicular development, rupture and progesterone levels above 15.0 nmol/L.

Cervical mucus

The mean maximum cervical mucus score for TCu380Ag users was 12.0 ± 0.8. Nine LNg-IUD users with type D cycles showed good cervical mucus score. For these LNg-IUD users cervical mucus score was 10.5 ± 0.9. This difference was not statistically significant compared with the TCu380Ag users. The amenorrheic women all had scanty and viscous mucus and the material was insufficient for study.

Levonorgestrel levels

The mean levonorgestrel level in the LNg-IUD users was 0.41 ± 0.01 nmol/L (mean $\pm$ SE) (Figure 3).

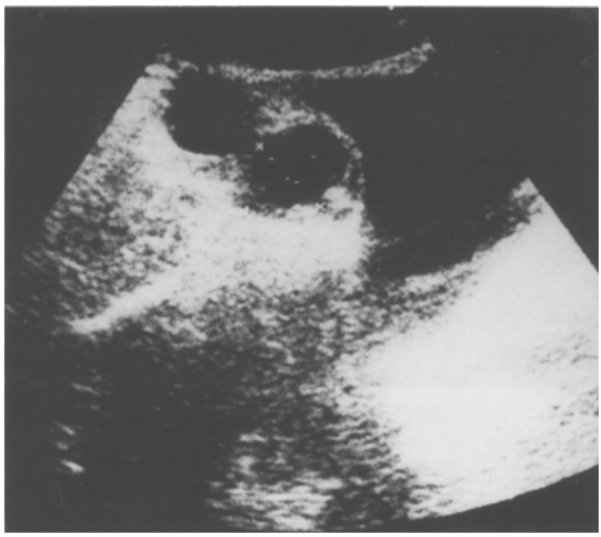

Figure 2. A typical representation of two unruptured follicles from a woman who had used a LNg-IUD for more than seven years. This picture was taken on day 21 of the cycle when the progesterone level was 19.5 nmol/L

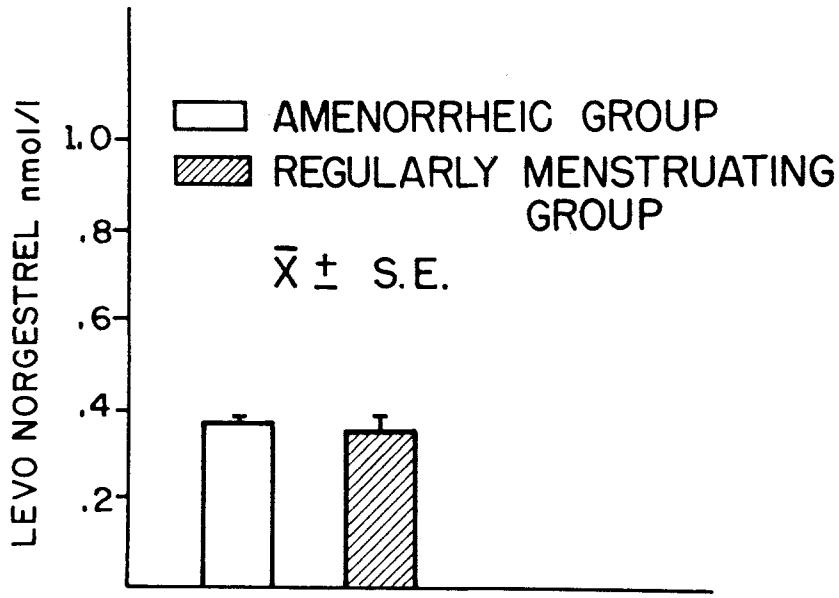

Figure 3. Plasma levels of levonorgestrel in women who have used the LNg-IUD for more than seven years. There is no statistically significant difference between regularly menstruating and amenorrheic women

SHBG capacity

The mean SHBG capacity for TCu380Ag users was 59.4 ± 2.8 nmol/L and for the levonorgestrel users, it was 46.0 ± 1.0 nmol/L. This difference was statistically significant ($p < 0.001$).

Discussion

Previous studies in women using levonorgestrel-releasing implants, Norplant [13,14], for more than three years, showed that 20% of the women had luteinization of unruptured follicles (LUF). This is in agreement with the finding that low doses of progestogen-only methods induce abnormal follicular development [15]. Disturbances in follicular development and rupture have also been observed in LNg-IUD users [8,16]. Luteinization of unruptured follicles and other disturbances in follicular development and rupture were also observed in women with insufficient luteal phase and unexplained infertility [17–22].

In the present study, ovarian function was studied in detail. In LNg-IUD users after seven years of use, disturbances in follicular development and rupture were observed despite the fact that there was no statistically significant difference in hormonal levels compared to the controls. This suggests that subtle hormonal changes affecting ovarian function may result from the continuous release of levonorgestrel from these IUDs.

Progesterone levels in LNg-IUD users were lower than in the TCu380Ag users, but this difference was not statistically significant. The presence of good cervical mucus score in 69% of the ovulatory cycles studied in LNg-IUD users indicates that effect on cervical mucus cannot be the main mechanism of action in these women. A significant decrease in SHBG levels was observed compared with the controls. This is in accordance with previous studies [8]. The levels of levonorgestrel after seven years of LNg-IUD use were similar to the same levels observed in our previous study after four years of use [8]. Levonorgestrel, though present in low concentrations, causes disturbances in follicular growth and rupture, as detected by ultrasound. Some studies have shown that progestins can be luteolytic in women [23,24].

Previous studies suggest that the suppressive effect of the LNg-IUD on endometrial growth accounts for the amenorrhea that was observed in some patients despite the fact that progesterone levels, as an indication of ovarian activity, could be detected in blood [4,25,26].

A report from Luukkainen et al. and Nilsson et al. suggests that the main mechanism of action of LNg-IUD is a local inhibitory effect on cervical mucus and on endometrial growth. According to their studies, levonorgestrel IUD does not cause disturbances in follicular development of the ovaries [3,6].

The previous studies by Nilsson et al. [6] that LNg-IUD users had normal ovarian function is not in agreement with our findings. Even though we were able to detect luteal progesterone levels in almost 90% of the cycles studied, ultrasound has shown a great number of disturbances of follicular maturation that were not detected in previous studies in LNg-IUD users.

Our findings suggest that the LNg-IUD may exert its contraceptive action in at least four different ways:

1. Inhibition of ovulation;

2. Endometrial changes preventing implantation;

3. Alterations of physical and chemical properties of cervical mucus, affecting sperm transport in some patients;

4. Subtle disturbances in hypothalamic pituitary ovarian function, resulting in disturbances of follicular growth and rupture.

The combination of one or more of these mechanisms may account for the high degree of antifertility action of this IUD.

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Resumé

Cette étude a porté sur 15 femmes présentant des cycles menstruels réguliers et 7 femmes aménorrhéiques qui utilisaient depuis plus de sept ans des DIU libérant du lévonorgestrel (DIU-LNg). Comme témoins, on a étudié pendant deux cycles menstruels complets 8 femmes qui portaient un dispositif TCu380Ag depuis plus de sept ans. La fonction ovarienne a été relevée par évaluation hormonale et par des examens aux ultrasons. Celles dont les menstruations étaient régulières ont été étudiées pendant deux cycles complets et les femmes aménorrhéiques pendant 8 semaines.

D'après les niveaux de progestérone, chez les utilisatrices de DIU-LNg ayant des menstruations régulières, 93% des cycles étaient ovulatoires mais seulement 58% de ces cycles 'ovulatoires' présentaient une croissance folliculaire normale avec rupture. Des kystes folliculaires et la lutéinisation des follicules en régression ont été observés dans 42% des 26 cycles 'ovulatoires'.

L'importance des SHBG était diminuée chez les utilisatrices du DIU-LNg comparée à celle des utilisatrices du TCu380Ag. Les niveaux de progestérone étaient plus faibles chez les premières que chez les secondes mais la différence n'était pas statistiquement significative. Les niveaux préovulatoires d'oestradiol et d'hormone lutéinisante étaient inférieurs dans le groupe LNg, sans que la différence ne soit statistiquement significative.

En ce qui concerne les femmes aménorrhéiques, 5 présentaient des kystes folliculaires qui disparaissaient

spontanément en 45 jours. Chez deux patientes, on a observé le développement et la rupture des follicules.

Dans 69% des cycles ovulatoires étudiés chez les utilisatrices du DIU-LNg, la présence de mucus cervical était bonne, ce qui laisse penser que les effets sur le mucus cervical ne peuvent être le principal mode d'action de ces dispositifs.

Il en est conclu que les DIU-LNg exercent sans doute un effet contraceptif de nombreuses manières, telles que l'inhibition de l'ovulation, des modifications de l'endomètre empêchant l'implantation, l'altération des propriétés physiques et chimiques du mucus cervical qui a une incidence sur le transport du sperme, et de légères perturbations de la fonction ovarienne hypothalamo-pituitaire, qui entraîne des modifications dans le développement et la rupture des follicules.

Resumen

Se estudiaron quince mujeres con períodos menstruales regulares y siete mujeres amenorreicas que habían estado utilizando un DIU de descarga de levonorgestrel durante más de siete años. Como controles, se estudiaron a 8 mujeres que utilizaban DIU TCu380Ag desde hacía más de siete años durante dos ciclos menstruales completos. Se evaluó la función ovárica mediante determinación hormonal y exámenes de ultrasonido. Las mujeres que menstruaban regularmente fueron estudiadas durante dos ciclos menstruales completos y las mujeres amenorreicas durante 8 semanas.

Según los niveles de progesterona, en las usuarias de DIU con LNg que menstruaban regularmente el 93% de los ciclos eran ovulatorios pero sólo el 58% de estos ciclos 'ovulatorios' señalaban un crecimiento y ruptura folicular normal. Se observaron quistes foliculares y luteinización de los folículos regresivos en el 42% de los 26 ciclos 'ovulatorios' estudiados.

La capacidad SHBG se había reducido en las usuarias de DIU con LNg en comparación con las usuarias de TCu380Ag. Los niveles de progesterona eran inferiores en las usuarias de DIU con LNg que en las usuarias de TCu380Ag pero esta diferencia no era estadísticamente significativa. Los niveles preovulatorios de estradiol y LH eran inferiores en las usuarias de DIU con LNg que en las usuarias de TCu380Ag. Estas diferencias no eran estadísticamente significativas. Entre las mujeres amenorreicas, 5 tenían quistes foliculares que desaparecieron espontáneamente dentro de los 45 días. Dos mujeres señalaron desarrollo y ruptura folicular.

La presencia de buen moco cervical se observó en el 69% de los ciclos ovulatorios estudiados entre las usuarias de DIU con LNg. Esto indica que los efectos sobre el moco cervical no pueden ser el principal mecanismo de acción de los DIU con LNg.

Se llega a la conclusión de que los DIU con LNg pueden ejercer un efecto anticonceptivo de muchos modos diferentes, tales como la inhibición de la ovulación, cambios del endometrio que impiden la implantación, alteración de las propiedades fisicoquímicas del moco cervical que afectan el transporte de esperma y perturbaciones sutiles de la función ovárica pituitaria hipotalámica que originan alteraciones del desarrollo y la ruptura folicular.