

Original research article

Serum levonorgestrel levels and endometrial thickness during extended use of the levonorgestrel-releasing intrauterine system

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Abstract

Background: The levonorgestrel-releasing intrauterine system (LNG-IUS) is a contraceptive method approved for five years of use. However, there is some evidence that its life span may be longer. The aim of the study was to evaluate serum levonorgestrel (LNG) and estradiol (E_2) levels and endometrial thickness every 6 months from 7 to 8 1/2 years after insertion.

Study Design: At the end of the approved 5-year life span, no replacement devices were available; therefore, 86 women were allowed to retain the same device for a further 2 years. At the 7-year follow-up visit, the women who consented were again allowed to retain the same device for a further 18 months and were followed-up at six-monthly intervals. At each visit, vaginal sonography was performed to measure endometrial thickness, and a blood sample was taken to measure LNG and E_2 .

Results: Eighty-four months after insertion, 67 women aged 34.3 ± 0.8 years (mean \pm SEM) (range, 25–49 years) returned for follow-up. Mean \pm SEM LNG levels decreased from an initial 253 ± 27 pg/mL (range, 86–760) during the first 2 months following insertion to 137 ± 12 (range, 23–393) at 84 months and 119 ± 9 pg/mL (range, 110–129) at 102 months of use (\pm SEM). At 84 months of use, mean \pm SEM endometrial thickness was 2.8 ± 0.1 mm, increasing to 3.8 ± 0.5 mm at 102 months of use. The incidence of amenorrhea decreased from 41.8% at 84 months to 31.5% at 102 months of use. No correlation was found between LNG levels and bleeding patterns; however, a weak correlation was found between high body mass index (kg/m^2), high weight, and low serum LNG levels. E_2 levels were similar to those of the follicular phase of the menstrual cycle of regularly menstruating women.

Conclusions: During extended use of the LNG-IUS, serum LNG levels were nearly half those found in the first 2 months of use (Wilcoxon signed rank test); serum E_2 levels were normal. Despite the very thin endometrium, menstrual bleeding was reinstated in many cases. At the end of its 5-year life span, there is a window for changing the LNG-IUS, and physicians and users should not be concerned about delaying replacement of the device for a short time beyond the approved life span; however, maintaining the same device long after its approved life span cannot be recommended.

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1. Introduction

Long-term contraceptive methods are desired by many women because they provide contraception without the requirement of having to remember to take a daily pill or a monthly or three-monthly injection. Long-term methods include subdermal implants, intrauterine devices and the levonorgestrel-releasing intrauterine system (LNG-IUS).

The LNG-IUS is marketed and approved in 123 countries for use as a contraceptive method. One of the effects of the use of the LNG-IUS is amenorrhea caused by the antiproliferative effect of levonorgestrel (LNG) on the endometrium [1–3]. As a consequence of this effect, the device has been approved and is currently in use in many countries as a treatment for idiopathic menorrhagia [4,5] and as endometrial protection during estrogen therapy [6,7]. In addition, this device has been used off-label as a treatment for endometriosis [8,9] and for endometrial hyperplasia [10,11].

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The LNG-IUS is approved for 5 years of use during which time the device provides high contraceptive efficacy with few adverse effects [1,12]. Some limited data exist on the device's extended use beyond 5 years and up to 7 years [2,13,14]. The objectives of this study were to evaluate the serum levels of LNG and estradiol (E_2) and the endometrial thickness of women who used the LNG-IUS beyond its approved life span of 5 years.

2. Materials and methods

The study was conducted at the Human Reproduction Unit, Department of Obstetrics and Gynecology, School of Medical Sciences, Universidade Estadual de Campinas, Campinas, Brazil. The ethical committee of the university approved the study, and all participants signed an informed consent form prior to admission.

The study population consisted of a subsample from a larger group of women participating in an acceptability study of the LNG-IUS (Mirena®, Bayer Schering Pharma Oy, Turku, Finland) in Brazil who had their devices inserted between April and September 1998 [3,15]. At the end of the approved 5-year life span of the device, no new devices were available to replace the ones in use; therefore, any woman who wished to do so were allowed to retain the same device for a further 2 years. At the 7-year follow-up visit, the women in the extended use protocol were once again allowed to retain the same device for a further 18 months and were invited to return for follow-up visits at six-monthly intervals. At each visit, the threads of the LNG-IUS were visualized during a gynecological examination. Next, ultrasonography was performed using a 6.0-MHz vaginal probe (Justavision 400, Toshiba, Toshihi-Ken, Japan) to measure double-layer endometrial thickness and to be sure that the LNG-IUS was located in the uterine fundus. A blood sample was then collected, and the serum was separated and stored at -20°C until assayed. Weight for each woman was evaluated at each follow-up visit and body mass index (BMI, kg/m^2) was calculated. Also, we reviewed and retrieved the

data from the menstrual calendar kept by each woman during the 90 days preceding the interview. According to the World Health Organization [16,17], bleeding was defined as “any bloody vaginal discharge that requires the use of protection such as pads and tampons” and spotting as “any bloody vaginal discharge that is not intense enough to require sanitary protection”. Amenorrhea was defined as no bleeding during the preceding 90 days before the interview and oligomenorrhea as bleeding episodes with more than 35 days interval.

Serum samples from women who had insertion of an LNG-IUS in 1998 had been collected at the first scheduled follow-up visit after insertion, and aliquots were kept in the freezer. In this clinic, the first follow-up visit was generally scheduled 30–50 days after insertion. Blood was collected 27–50 days following insertion. Follow-up visits were carried out at six-monthly intervals from 84 months until 102 months after insertion.

2.1. LNG and E_2 assay

Serum LNG levels were measured using a validated method of high-performance liquid chromatography coupled with tandem mass spectrometry. All procedures were carried out in compliance with the guidelines approved by the Brazilian regulatory authorities (ANVISA) for Good Laboratory Practices. The LNG standards used in the assay were obtained from USP (Rockville, MD, USA). Biological specificity of the method was checked by processing independent serum samples and blank samples obtained from women not using any kind of hormones.

Briefly, the bioanalytical assay for the quantification of LNG was developed using an online solid phase extraction method (Symbiosis, Spark Holland, Emmen, The Netherlands). The mass spectrometer (Sciex/Applied Biosystems, model API5000, Toronto, Canada) was equipped with a photo-ionization source (APPI) running in positive ion mode setup in Multiple Reaction Monitoring for the transition m/z 313.3 245.1 for LNG. Toluene was used as solvent at the flow rate of 0.15 mL/min. The lowest limit of quantification of the method was 20 pg/mL, and it was linear over the range

Table 1
Serum LNG levels (pg/mL) and endometrial thickness (mm) at different times after insertion of the LNG-IUS

Time after insertion	Age at blood collection	LNG (pg/mL)			Endometrial thickness (mm)		E_2 (pg/mL)	
		Mean±SEM	n^a	Range	n	Mean±SEM	n	Mean±SEM
Days								
27–50	33.4±0.71	86	253±27	86–760			86	99.2±11.4
Months								
84	34.3±0.75	67	137±12	23–393	67	2.79±0.1	67	86.1±10.4
90	35.2±1.00	51	130±11	18–470	55	3.31±0.2	58	103.0±15.3
96	34.4±1.20	25	132±18	51–505	35	3.75±0.3	34	103.0±20.9
102	41.5±3.50	2 ^b	119±9	110–129	8 ^b	3.76±0.5	8 ^b	93.6±29.8

Friedman test for repeat samples and Wilcoxon signed rank test only to compare LNG values at Days 27–50 with other values.

^a These figures indicate the number of cases both for age and LNG measurements.

^b In six samples we were unable to measure LNG due to technical problems.

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