

Original research article

# Predictors of oligoamenorrhea at 1-year follow-up in premenopausal women using a levonorgestrel-releasing intrauterine system

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## Abstract

**Objective:** The study was conducted to identify predictors of oligoamenorrhea at 12 months in levonorgestrel-releasing intrauterine system (LNG-IUS) users.

**Design:** A 12-month observational study.

**Setting:** Gynecologic outpatient clinic in a large regional hospital in Flanders, Belgium.

**Population or Sample:** A total of 150 women who had made an informed decision to use a LNG-IUS either as a method of contraception or to manage menorrhagia.

**Methods:** All women were premenopausal and first-time users. The variables recorded prior to insertion on Days 1 to 5 of the menstrual cycle were age, parity, body mass index, indication for LNG-IUS use, prior contraceptive use, menstrual bleeding history, length of the uterine cavity, endometrial thickness, number of antral follicles, serum follicle-stimulating hormone, inhibin B and anti-Müllerian hormone. Menstrual bleeding pattern, patient satisfaction or wish to discontinue the method was noted at 3, 6 and 12 months of follow-up visits.

**Main Outcome Measures:** Menstrual bleeding pattern (amenorrhea, oligomenorrhea, menorrhagia) at 12 months was taken as the primary outcome measurement. Patient satisfaction was followed as a secondary outcome.

**Results:** Oligoamenorrhea was associated with a high patient satisfaction. A bleeding period less than 5 days, absence of severe uterine bleeding at baseline, LNG-IUS use for contraception and oligoamenorrhea at 3 months were predictors of a favorable outcome at 12 months in a univariate analysis. The absence of severe bleeding prior to LNG-IUS insertion was the only clinically useful predictor of favorable outcome in the multivariate analysis (odds ratio 0.13, 95% confidence interval 0.02–0.66).

**Conclusions:** Patient profiling as described is not helpful in counselling women for intentional LNG-IUS use, especially not if it is planned as a method of managing menorrhagia.

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**Keywords:** Levonorgestrel-releasing intrauterine system; Treatment; Contraception; Prognosis

## 1. Introduction

The levonorgestrel-releasing intrauterine system (LNG-IUS) is commonly used for both contraceptive [1] and noncontraceptive indications [2,3], such as the management of menorrhagia [4]. Women expect to be offered a high degree of therapeutic success before they accept and comply with any treatment modality [5]. This need for a degree of certainty in treatment outcome was partially

responsible for the poor patient recruitment in the SMART study in which women were randomized between either endometrial ablation or LNG-IUS [6]. Excessive or irregular bleeding is the single most important reason for removal of the LNG-IUS [7,8]. Therefore, counselling about the potential changes in the menstrual pattern, such as amenorrhea and bleeding irregularities induced by the use of the LNG-IUS, will improve patient compliance [9,10]. However, little is known about the predictive factors affecting menstrual bleeding after insertion of an LNG-IUS. We conducted this study to identify predictors of bleeding pattern in the first year of LNG-IUS use in

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order to improve pre-insertion counselling and hopefully patient satisfaction with their therapeutic choice.

## 2. Materials and methods

Between September 2004 and December 2005, premenopausal women recruited from the outpatient clinic were entered in this observational study after their informed choice to have an LNG-IUS inserted either for contraceptive reasons or for the treatment of subjective menorrhagia. The objective of the study was to identify factors prior to insertion of the LNG-IUS that were associated with oligomenorrhea at 12 months' follow-up. Women were considered eligible for inclusion if they were between 18 and 45 years of age, first-time users, premenopausal and more than 6 months postpartum, had no medical contraindication to the use of an LNG-IUS, were not on any anticoagulant therapy and had signed an informed consent form. Women with uterine fibroids, endometrial or ovarian pathology, or abnormal cervical cytology were excluded. The LNG-IUS was inserted within the first 5 days of the menstrual cycle. The following variables were recorded upon entry in the study prior to LNG-IUS insertion: age, parity, body mass index, prime indication for LNG-IUS use (contraception or management of menorrhagia), prior contraceptive use, changes in contraceptive method in the past, menstrual bleeding history (duration of menstruation, objective signs of excessive bleeding such as loss of red-stained blood, formation of large blood clots, need for extra sanitary protection), the length of the uterine cavity and the double-layer thickness of the endometrium, and, as a selection of parameters of ovarian reserve, the number of antral follicles was measured on ultrasound and the presence of five or more antral follicles (more or less than five follicles) [11], basal serum follicle-stimulating hormone (FSH) [12], inhibin B [13] and anti-Müllerian hormone (AMH) [14]. Serum FSH was assessed using a chemiluminescent assay (ADVIA Centaur, Bayer Diagnostics, Germany) with an intra- and inter-assay variation of 2.3% and 4%, respectively, and a sensitivity of 0.3 mIU/mL. Serum inhibin B was measured using an enzyme-linked immunosorbent assay (MCA1312KZZ, Serotec, Oxford, UK) with an intra- and inter-assay variation of 4.4% and 7.8%, respectively, and a sensitivity of <15 pg/mL. Serum AMH was measured using an enzyme-linked immunosorbent (ELISA) kit (DSL-10-14400 ELISA, Beckman-Coulter/DSL, Texas, USA) with an intra- and inter-assay variation of 3.4% and 6.5%, respectively, and a sensitivity 0.006 ng/mL. All collected samples for inhibin B and AMH were measured in two separate assays on the same day. FSH samples were measured in the same assay on the same day.

Women were seen at 3-, 6- and 12-month follow-up visits, and menstrual bleeding pattern, patient satisfaction and wish to discontinue the method were noted. Women in whom the

LNG-IUS was expelled or removed were considered to be dissatisfied for the duration of the study.

Amenorrhea was defined as the absence of bleeding for at least 3 months; oligomenorrhea as the presence of scanty bleedings with an interval of 6 weeks or more.

All statistical analyses were based on the intention-to-treat principle. Student's *t* tests and Fisher's exact tests were used where appropriate. Generalized estimating equations methodology, a correlation-corrected logistic regression analysis, was fitted to the repeatedly observed bleeding pattern binary outcome (oligoamenorrhea vs. menorrhagia) to identify, in a conventional univariate fashion, predictors of bleeding pattern at 12 months [15,16]. A multiple logistic regression model was used to test the association between the bleeding pattern at 12 months and possible predictive factors defined at the onset of the study. All variables with  $p < .05$  in the univariate analysis were entered in the multivariate regression model, and a standard backward stepwise procedure was used. The Hospital Ethics Committee approved the study protocol.

## 3. Results

A total of 153 women were entered in the study. Three women were excluded from analysis as they were not first-time users (inclusion violation). Of the remaining 150 women analyzed, 141 women completed a 12-month monitoring period: there was no follow-up at all in four women, one woman was lost to follow-up after 3 months and four women were lost to follow-up after 6 months (the mean follow-up time of the cohort was  $10.9 \pm 2.6$  months). The primary indication for insertion was contraception in 98 and management of excessive bleeding in 52 women. Women in the contraception group were younger (33.9 vs. 39.1 years,  $p < .0001$ ) and had less subjective bleeding abnormalities (20.0% vs. 96.1%,  $p < .0001$ ). In three women, the LNG-IUS was expelled (after 3, 5 and 6 months) and in one of them it was replaced. A total of 18 women (3 women at a late stage at 12 months) discontinued for various reasons: unacceptable bleeding (10, of whom 3 had a hysterectomy), pelvic pain (3), pelvic inflammatory disease (2), wish for tubal ligation (1), amenorrhea and emotional discomfort (1) and acne (1). Women had a mean age of 35.7 years (SD 6.8) and a parity of 1.9 (SD 0.4). Further baseline characteristics of the population recorded on the day of insertion were mean BMI 24.5 (SD 4.2), uterine cavity length of more than 7 cm in 60.3% of women and double layer endometrial thickness of 4 mm or more in 63.5% of women. Regarding the baseline characteristics of ovarian reserve, we found that 74.5% of women had less than five follicles and we recorded mean serum concentration values of 7.53 mIU/mL (SD 5.19), 68.73 pg/mL (SD 48.68) and 1.13  $\mu$ g/L (SD 1.42) for FSH, inhibin B and AMH, respectively.

Predictors of oligomenorrhea at 12 months are presented in Tables 1 and 2. LNG-IUS users most likely to have a good outcome had a menstrual period less than 5 days prior to

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