Title: One year quality of life measured with SEC-QoL in levonorgestrel 52 mg IUS users

Running title: Quality of life with LNG-IUS

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Abstract

Objectives: The present study aims to prospectively evaluate quality of life (QoL) of women using 52 mg levonorgestrel intrauterine system for contraception determined through the SEC-QoL, a questionnaire specifically designed to assess the impact of contraceptive methods on QoL of fertile women.

Study design: We conducted a prospective observational multicenter study of 201 reproductive age women who initiated the levonorgestrel intrauterine system (LNG-IUS) for contraception. Sociodemographic and clinical data were collected at baseline and 12 months afterwards. Participants filled in the SEC-QoL questionnaire at both visits. SEQ-QoL scores range from 0 (worst QoL) to 100 (best QoL).

Results: Participants claimed an increased QoL 12 months after insertion in all five dimensions of SEC-QoL due to its high contraceptive efficacy and its capability to reduce other menstrual symptoms (e.g. heavy menstrual bleeding or dysmenorrhoea), overall exerting a positive impact on user's satisfaction. SEC-QoL general overall score went from a mean (SD) score of 46.3 (17.3) at baseline to 72.2 (14.8) 12 months afterwards ($p<0.001$). Overall, 94.6% of women claimed having found additional benefits other than contraception. No pregnancies were reported during the 12 months of study duration and only 14 women discontinued use of LNG-IUS (only two of them due to an adverse event), representing a continuation rate of 93%.

Conclusions: Women using LNG-IUS for contraception have an increased QoL after 12 months of use, demonstrated by the increased score in all dimensions of the SEC-QoL questionnaire.

Implications:

The present study prospectively evaluated QoL of women using LNG-IUS for contraception through the SEC-QoL questionnaire. Participants claimed increased QoL 12 months afterwards, implying that women using LNG-IUS for contraception

in usual clinical practice also benefit from the reduction of period-related symptoms, overall leading to very low discontinuation rates.

Key Words: Intrauterine System / Levonorgestrel / Quality of Life / Contraception / SEQ-QoL questionnaire

1. Introduction

Levonorgestrel intrauterine system (LNG-IUS) exhibits a very low discontinuation rate and very good level of satisfaction within its users [1–3]. Particularly, several studies reveal that benefits associated to LNG-IUS are not only related to its contraception efficacy [4], but are also due to its capability to reduce other menstrual and premenstrual symptoms [5,6] which exert a negative impact on women's health related quality of life (HRQoL) [7–10]. Given the benefit provided by LNG-IUS in the reduction of heavy menstrual bleeding (HMB), the National Institute for Health and Care Excellence (NICE) institute in the UK recommended it as first line treatment for HMB in 2007 [11], and the Food and Drug Administration (FDA) approved its use for this indication in 2009.

Several studies have been conducted to assess HRQoL in women using LNG-IUS to reduce HBM [12,13]; as well as for women using it for contraception [14–16], in which HRQoL was assessed through generic questionnaires (i.e. EQ-5D or SF-36) [17].

However, to the best of our knowledge, there is a lack of studies aiming to determine the level of satisfaction and HRQoL of women using LNG-IUS for contraception, particularly, those in which HRQoL was assessed through questionnaires specifically designed for fertile women under contraception like the SEC-QoL questionnaire [18].

In this context, the present study aims to assess the impact of 52 mg LNG-IUS used for contraception on HRQoL of women, after 12 months of use through the SEC-QoL questionnaire in Spain.

2. Material and methods

2.1 Study design

We conducted a prospective observational multicenter study of 201 reproductive age women who initiated the 52 mg LNG-IUS for contraception. The cohort included women aged from 18 to 49 who were recruited from 18 private gynaecological centres in Spain, after giving written informed consent. Women were eligible to participate in this study unless they (i) presented contraindications for LNG-IUS, (ii) were using LNG-IUS for non-contraceptive purposes such as HMB, (iii) had used any other kind of hormonal contraceptives 3 months prior to study inclusion, (iv) were unable to fill in the study questionnaire, (v) were participating in other clinical trials. The study was conducted following current Spanish regulations for post-authorization studies, and was approved by the Spanish Agency of Medicine and Health Products and the Hospital *la Zarzuela* Research Ethic Committee.

The present study consisted of two visits: when starting use of LNG-IUS (baseline) and 12 months afterwards (final visit). Sociodemographic and clinical data were collected from medical charts or from the interviews conducted during the study visits. At baseline (when LNG-IUS was introduced), the following sociodemographic data was collected: age, level of education, employment status and marital status. Both at baseline and final visits, the following clinical data was collected: bleeding intensity, painful menstrual periods (measured through a visual analogue scale (VAS) ranging from 0: "no pain" to 10: "maximum pain"), menstrual and premenstrual breast symptoms, and presence of non-contraception benefits from LNG-IUS (reduction of period-related symptoms, improvement of anaemia, improvement of skin and/or hair appearance, reduction of migraine episodes,

others). Period-related symptoms were assessed on the basis of women's personal perception. In order to determine HRQoL evolution of included women, they were asked to fill in, both at baseline (straight after introducing LNG-IUS) and at final visits, the self-administered SEC-QoL questionnaire [18]; a specific HRQoL questionnaire for fertile women on contraception which consists of 19 items distributed in five dimensions: "social" (5 items), "menstrual symptoms" (4 items), "breast symptoms" (3 items), "psychological" (4 items) and "sexual" (3 items); each item allowing for five liker-type response choices (from "always" to "never" or from "totally agree" to "totally disagree", depending on the kind of statement). Overall scores were obtained by adding up the responses from the corresponding items, which were subsequently standardised to a scale ranging from 0 (worst HRQoL) to 100 (best HRQoL). In addition, at the final visit, women were asked about their general level of satisfaction with the method using a VAS graded from 0 ("not satisfied at all") to 10 ("very satisfied").

2.2 Sample size

Sample size was calculated in order to detect changes in terms of HRQoL measured through the SEC-QoL questionnaire at baseline and final visits. According to the validation study of the SEC-QoL questionnaire, in which women initiating contraception went from a mean (SD) score of 46.6 (17.8) to 57.0 (18.4) [18], a minimal important difference (MID), the smallest change in score at baseline and final visits required to be considered clinically relevant, was established at 3.4 points. However, the SEC-QoL validation study included women using many different contraceptive methods, whereas in the present study only women using LNG-IUS were included, thus a more conservative approach was considered for the sample size calculation. In this context, in order to detect changes ≥5 between scores reported at baseline and final visits, assuming a deviation of 18, a significance level of 0.05, a statistical power of 0.8 and at least 10% of dropouts, a minimum sample of 150 women was estimated.

2.3 Statistical Analysis

All women fulfilling inclusion criteria were included in the analysis, except those who had not completed the SEC-QoL questionnaire at baseline. Women who discontinued the study and reason for discontinuation were also collected. A descriptive analysis of sociodemographic and clinical data and scores from the SEC-QoL questionnaire at baseline and final visits was conducted. Correlation between SEC-QoL results and sociodemographic and clinical variables was determined through the ANOVA test and Pearson correlation coefficient. The MID was established at 3.4 points for the overall score in the context of the validation of the SEC-QoL questionnaire [18]. Finally, impact of menstrual symptoms on HRQoL and the scores reported at each SEC-QoL dimension, was analysed through a lineal regression model. Statistical analysis was performed using the SAS system version 9.2 (SAS Institute Inc., Cary, NC, USA) in Windows™ operating system support. A level of statistical significance (p) of 0.05 was established for all correlations.

3. Results

Out of the 201 included women, 14 did not complete the entire study: 7 dropouts, 5 due to LNG-IUS discontinuation (2 due to an adverse event: bleeding between periods and abdominal discomfort; 2 because of device expulsion; and 1 due to willingness to become pregnant), 1 due to woman's personal opinion and 1 because of death or serious disease not related to the medication. Table 1 summarises some of the most relevant sociodemographic data. Mean (SD) age of participants was 38.7 (5.0). It is worth noting that more than 60% of included women had completed University education, 96.5% claimed having a stable partner at baseline, 95% had had at least one baby and 40% had carried two pregnancies to term. Regarding contraception methods used the year before starting use of LNG-IUS, the most common were condoms (51.7%), followed by combined oral contraceptives (17.9%).

In order to fulfil the primary objective of the present study, the SEC-QoL score evolution was analysed. At baseline, mean (SD) overall score was 46.3 (17.3), which increased to 72.2 (14.8) 12 months afterwards; scores in all dimensions experiencing a statistically significant improvement ($p<0.001$). Figure 1 shows the scores reported in all dimensions at baseline and 12 months afterwards. Moreover, when comparing the mean overall score reported at both visits, 91.7% of women experienced a positive and statistically significant evolution in terms of HRQoL, which corresponded to the percentage of scores that reached the MID established for this questionnaire at the validation process [18]. In addition, women who, according to their personal perception, claimed suffering HMB at baseline, reported lower scores in all SEC-QoL dimensions (<0.05). Similarly, increased painful menstrual periods related to lower scores from all SEC-QoL questionnaire dimensions ($p<0.005$).

Figure 1 also shows the *p* values for the correlation between changes in SEC-QoL scores between visits with changes in bleeding intensity and painful menstrual periods also between visits. As can be observed from figure 2, reduction of menstrual bleeding intensity did not exert a statistically significant effect on HRQoL ($p>0.05$ in all SEC-QoL dimensions), whereas reduction of painful menstrual periods did significantly correlate with an increased HRQoL ($p\leq0.007$ in all dimensions of the SEC-QoL).

Furthermore, during the 12 months of study duration, no pregnancies were reported and the overall level of satisfaction was 8.4. In addition, 94.6% of women claimed having found additional benefits associated to LNG-IUS other than contraception; participants reported having experienced a reduction of bleeding (90.9%), and menstrual (45.2%) and premenstrual (39.8%) symptoms. For instance, in spite of LNG-IUS being used for contraception, 58.2% of women

claimed having had HMB three months prior to the study inclusion (when they started using LNG-IUS), whereas none of them reported suffering it 12 months afterwards; 96.8% reporting limited or very limited bleeding ($p<0.001$). Furthermore, a reduction in painful menstrual periods was also reported; on a 0 (no pain) to 10 (maximum pain) scale, the mean (SD) score going from 3.8 (2.7) at baseline to 0.9 (1.3) at the final visit. Also, 44.8% of women reported scores between 4 and 10 at baseline, whereas 12 months afterwards, 87.6% of women reported scores below 2 (no pain). The aforementioned positive results translated into a very high continuation rate (93%).

4. Discussion

The present study assesses HRQoL of women using LNG-IUS for contraception through the only validated questionnaire specifically designed for fertile women using contraceptives, thus providing novel information on the effect of LNG-IUS on its 5 specific dimensions (social, menstrual symptoms, breast symptoms, psychological and sexual) that could not be assessed in previous studies as they employed generic questionnaires (i.e. SF-36 or EQ-5D) [12–17]. Thus, SEC-QoL has proved to be a unique and useful tool to assess changes in HRQoL in LNG-IUS users. Also, further reinforcing previously reported results [14–16], our findings conclude that women using LNG-IUS for contraception have increased HRQoL 12 months after insertion, which is reflected through an increased score in all five dimensions of the SEC-QoL questionnaire.

Moreover, participants claimed a high overall level of satisfaction (8.4 on a 0 to 10 scale); which again is consistent with previous studies, in which around 80% of women claimed being satisfied with LNG-IUS after a year of use [6,15]. However, caution should be taken when comparing level of satisfaction from different studies due to variability in the scale used for its evaluation.

Furthermore, participants claimed having experienced non-contraceptive benefits (i.e. reduction of bleeding, menstrual pain and general menstrual and pre-menstrual symptoms), which clearly had an effect on HRQoL. These benefits are consistent with those reported in previous studies which claimed that LNG-IUS significantly reduced painful periods and menstrual bleeding [6,15,19,20]; and also that these benefits were more commonly reported in women using LNG-IUS than in those using hormonal contraceptives, even to combined oral contraceptive pill [21,22].

In addition, consistently with previous results reported in terms of effectiveness and safety of LNG-IUS as a contraceptive method [1–3]; the lack of pregnancies being reported during the 12 months of study duration, together with the low discontinuation rate and the fact that only two women withdrew LNG-IUS due to an adverse event, further reinforce effectiveness and safety of LNG-IUS as a contraceptive method.

In the context of the SEC-QoL validation study, HRQoL of women using different contraceptive methods was assessed, both using a generic (EQ-5D) and specific questionnaire (SEC-QoL); and in spite of it leading to conclude that the SEC-QoL was a valid tool for use in clinical practice, the study only included 6 women using IUS [18]. In order to validate the SEC-QoL, the authors defined three study groups according to the type of contraceptive method of choice (effective, poorly effective or none). Women choosing effective contraceptive methods (hormonal contraceptives, consistent use of barrier methods, intrauterine devices, implants and injectables, male or female sterilization and dual methods) reported significantly higher level of education; similarly, a highly percentage of women participating in the present study claimed having University education (62.8%). Also, the SEC-QoL validation study concluded that women using effective contraceptives (mainly hormonal) reported higher scores, in all dimensions of SEC-

QoL (better HRQoL) compared to women using none or poorly effective methods. Mean SEC-QoL scores were lower than those reported at the final visit of the present study.

Despite real-life studies being necessary to confirm results from controlled clinical trials, the lack of intense monitoring or a control group may restrict the validity of their findings, thus representing a study limitation. Also, unlike previous studies in which the level of menstrual bleeding was measured through specific tests [23], in the present study period-related symptoms were assessed through women personal perception which may difficult comparison of our findings with previous studies due to interpersonal perception variability.

One of the main strengths of the present study is the methodology applied. A questionnaire specifically designed for fertile women using contraceptives has been used (SEC-QoL) which strengthens the validity of our findings. Also, two study visits have been included, when initiating use of LNG-IUS and 12 months afterwards, which has allowed the evaluation of HRQoL, satisfaction and menstrual symptoms evolution. However, another limitation of the present study is that HRQoL of women who discontinued the study was not assessed as they did not attend the final visit, thus, albeit small, the potential reduction of SEC-QoL mean score due to adverse events (n=2) or LNG-IUS expulsion (n=2) was not evaluated. Also, another possible limitation is that no interim visit was performed (i.e. 2-3 months after insertion), which would have provided interesting data on HRQoL shortly after LNG-IUS insertion.

The present study concludes that LNG-IUS exerts a positive impact on women's HRQoL and satisfaction, both because it provides its users with additional non-contraceptive benefits and due to its effectiveness and safety profile as a contraception method.

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6. Conflict of interest

I. Cristobal, I. Lete and E. De la Viuda received personal fees from Bayer Healthcare for conducting the study. N. Perulero is full-time employee of IMS Health. IMS Health received funding from Bayer Healthcare for conducting, analysing, and reporting the study. A. Arbat and I. Canals are full-time employees of Bayer Hispania.

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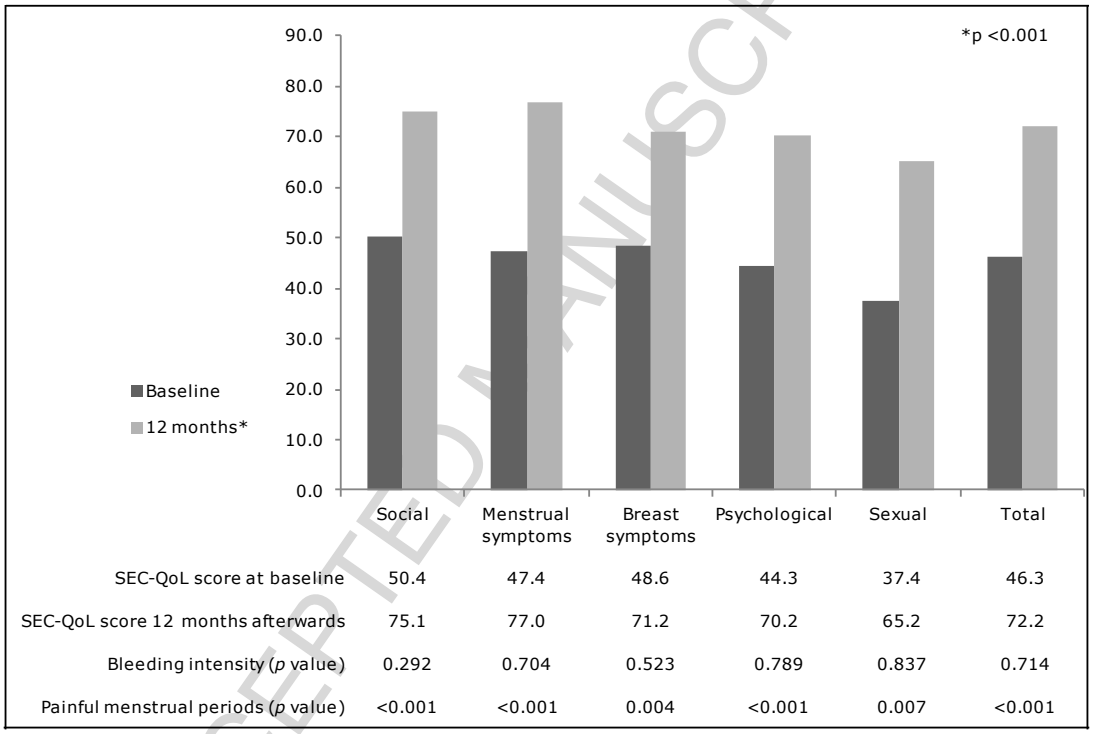
8. Tables

Table 1. Description of sociodemographic and clinical data.

Variable	Value
Age (years)	
Mean (SD)	38.7 (5.0)
< 35 years	20.7%
35-39 years	37.4%
40-44 years	27.3%
45-49 years	14.6%
Level of education	
Illiterate	1.5%
Primary education	10.6%
Secondary education	25.1%
University education	62.8%
Employment status	
Employed by other	65.8%
Self-employed	13.6%
Unemployed	8.0%
Housework	11.1%
Student	0.5%
Unknown	1.0%

9. Figures

Figure 1. Changes in HRQoL between baseline and final visit (scores from SEC-QoL) and statistical significance (p) between changes in SEC-QoL scores and symptoms.



	Social	Menstrual symptoms	Breast symptoms	Psychological	Sexual	Total
SEC-QoL score at baseline	50.4	47.4	48.6	44.3	37.4	46.3
SEC-QoL score 12 months afterwards	75.1	77.0	71.2	70.2	65.2	72.2
Bleeding intensity (*p* value)	0.292	0.704	0.523	0.789	0.837	0.714
Painful menstrual periods (*p* value)	<0.001	<0.001	0.004	<0.001	0.007	<0.001