Control of endometriosis-associated pain with etonogestrel-releasing contraceptive implant and 52-mg levonorgestrel-releasing intrauterine system: randomized clinical trial

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Objective: To assess the efficacy of an etonogestrel (ENG)-releasing contraceptive implant or the 52-mg levonorgestrel-releasing intrauterine system (LNG-IUS) in the control of endometriosis-associated pelvic pain.
Design: Noninferiority randomized clinical trial in which women with endometriosis were assigned to use an ENG implant (experimental treatment) or an LNG-IUS (active comparator). Monthly follow-up visits were conducted up to 6 months.
Setting: University teaching hospital.
Patient(s): One hundred three women, with endometriosis-associated chronic pelvic pain, dysmenorrhea, or both for more than 6 months. In cases of deep endometriosis, vaginal ultrasonography and magnetic resonance imaging were used as additional diagnostic tools.
Intervention(s): The ENG implant or the LNG-IUS were inserted within the first 5 days of the menstrual cycle.
Main Outcome Measure(s): Daily scores of noncyclic pelvic pain and dysmenorrhea were evaluated using a daily visual analogue scale. Health-related quality of life was evaluated using the Endometriosis Health Profile-30 questionnaire at baseline and up to 6 months. Bleeding patterns were assessed daily from a menstrual calendar.
Result(s): Both contraceptives improved significantly the mean visual analogue scale endometriosis-associated pelvic pain and dysmenorrhea, without significant differences between treatment group profiles. Health-related quality of life improved significantly in all domains of the core and modular segments of the Endometriosis Health Profile-30 questionnaire, with no difference between both treatment groups. The most common bleeding patterns at 180 days of follow-up were amenorrhea and infrequent bleeding and infrequent bleeding and spotting among ENG implant and LNG-IUS users, respectively.
Conclusion(s): In this noninferiority study both contraceptives improved significantly pelvic pain, dysmenorrhea, and health-related quality of life in endometriosis.
Clinical Trial Registration Number: Clinicaltrials.gov under number NCT02480647. (Fertil Steril® 2018;110:1129–36. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Endometriosis, etonogestrel-releasing contraceptive implant, levonorgestrel-releasing intrauterine system, pelvic pain

Received December 20, 2017; revised July 5, 2018; accepted July 6, 2018.
L.B. received an honorarium to be a member of an advisory board and has been an invited speaker at scientific meetings for Bayer Healthcare Pharmaceuticals and Merck, and is a member of the ICA Foundation without remuneration. C.L.B.-P. has been an invited speaker at scientific meetings for Bayer Healthcare Pharmaceuticals. N.C. has nothing to disclose. D.M. has nothing to disclose. K.C. has nothing to disclose.
This study received partial financial support from São Paulo Research Council awards 2015/20504-9 and 2015/10021 and from Brazilian National Research Council grant 573747/2008-3. Merck, the Netherlands also provided funds for the study under unrestricted grant 37228. The LNG-IUSs used in this study were donated by the International Contraceptive Access Foundation, Turku, Finland under an unrestricted grant. The donors did not have any participation in the elaboration of the protocol, conducting the study, analyzing the data, or writing the manuscript.
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Fertility and Sterility® Vol. 110, No. 6, November 2018 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2018.07.003

Pelvic pain is a major concern of women affected by endometriosis because it can be severe and exert a negative impact on health-related quality of life (HRQoL). Several surgical and medical treatments (1–3) have been proposed. Although several studies have reported an improvement in endometriosis-associated pelvic pain with the use of the levonorgestrel-releasing intrauterine system (LNG-IUS) (4, 5), few studies have evaluated the use of the etonogestrel (ENG) contraceptive subdermal implant for this purpose (6, 7).

Considering that one of the main objectives of the clinical treatment of endometriosis is pain control and not necessarily to achieve regression to a less severe stage of the disease or remission of its associated lesions, the efficacy of medical treatments depends on long-term therapeutic regimens with a minimum of side effects and good tolerability. In this respect, both the ENG implant and the LNG-IUS could play a significant role in the control of this disease. Therefore, the objective of this study was to compare the effectiveness of the ENG implant vs. the 52-mg LNG-IUS for the improvement of endometriosis-associated noncyclic pelvic pain, dysmenorrhea, and HRQoL in women with diagnosis of endometriosis.

MATERIALS AND METHODS

Study Design

This was an open-label, parallel-group, noninferiority randomized clinical trial (RCT) conducted at the Department of Obstetrics and Gynecology, University of Campinas Faculty of Medical Sciences, Campinas, São Paolo, Brazil between June 2016 and August 2017. The ethics committee approved the study protocol, and all the women signed an informed consent form before their admission to the study. The trial was registered at Clinicaltrials.gov under number NCT02480647.

Patients

Patients referred to the Department with a surgically and histologically confirmed diagnosis of stage I–IV endometriosis based on the Revised American Fertility Society Classification of Endometriosis (8) or women with a diagnosis of deep endometriosis according to transvaginal ultrasonography and magnetic resonance imaging (9, 10) and complaints of noncyclic chronic pelvic pain and dysmenorrhea or both for more than 6 months (11) were invited to participate in the study. Women who were clinically healthy, not pregnant, aged ≥ 18 and ≤ 45 years, able to keep a menstrual diary, willing to return to the clinic for follow-up visits, and willing to be randomized to the use of an ENG implant or an LNG-IUS, were included. Exclusion criteria for use of the ENG implant and for the LNG-IUS were those established by the World Health Organization (12). Additionally, women who had undergone surgical or hormonal treatments for endometriosis within 2 months of the enrollment in the study were excluded. All the insertions were performed within the first 5 days of the menstrual cycle. None of the women wished to conceive within the next 12 months.

Treatments

Women were randomized (1:1) to receive either the ENG-releasing contraceptive implant (Implanon NXT; Merck) (experimental treatment) or the 52-mg 20-μg/d LNG-IUS (Mirena; Bayer Oy) (active comparator). All women were followed up every 30 ± 3 days after device insertion up to 6 months after insertion or until removal or expulsion of the implant/LNG-IUS, whichever occurred first. The participating women were allowed to keep the ENG implant or the LNG-IUS after completion of the study, and they are being followed for up to 3 years after study initiation.

Randomization

The randomization sequence was generated using a computer program and a permuted block size of six. The information regarding which treatment was to be used was sealed inside opaque envelopes identified only by a number. The envelope was opened in front of the participant after she had signed the informed consent form, and the device was inserted immediately afterward.

Procedures

All participants received a pain score diary based on the visual analogue scale (VAS) for the assessment of noncyclic chronic pelvic pain and dysmenorrhea. The VAS scale is standardized from 0 (no pain) to 10 (in centimeters) (the worst pain imaginable) (11, 13). Participants recorded a daily score during the month preceding randomization to either the ENG implant or the LNG-IUS and during each month of follow-up. The monthly score was calculated as the result of the sum of the daily scores divided by the number of days in each observations period. A baseline pain VAS of at least 4 was required for inclusion in the study and defined as moderate and severe symptoms. Because many women do not present regular uterine bleeding after the ENG implant or the LNG-IUS placement, dysmenorrhea was reported as the discomfort or pain felt during irregular uterine bleeding episodes (14).

Bleeding patterns were assessed from a menstrual calendar provided to all participants. Data were analysed in 90-day reference periods, and patterns were classified as amenorrhea (no bleeding), infrequent bleeding (1 to 2 episodes of bleeding and/or spotting), frequent bleeding (>5 episodes of bleeding and/or spotting), regular bleeding (3–5 episodes of bleeding and/or spotting), prolonged bleeding (>14 consecutive days of bleeding and spotting), and spotting (>14 consecutive days of spotting alone) (15). Spotting was included as one of the bleeding patterns to acquire a better understanding of bleeding and spotting when prolonged.

Participants' HRQoL was evaluated using the Endometriosis Health Profile-30 (EHP-30) questionnaire (16, 17). This instrument is composed of two parts: a core questionnaire consisting of five scales with which to evaluate pain, lack of control or powerlessness, emotional well-being, social support, and self-image. This part includes 30 questions. A second part consists of a modular

questionnaire containing a total of 23 questions specifically related to the effect of endometriosis on the woman's work, sexual intercourse, and her relationship with her children, and her feelings about the medical profession, her endometriosis treatment, and infertility-related problems. Items within the scales are added together to reach a total score, and each scale is thus expressed as a score ranging from 0 to 100, with 0 reflecting the best possible QoL and 100 the worst.

Outcomes

The primary outcome was change in endometriosis-associated noncyclic pelvic pain and dysmenorrhea (18) evaluated by VAS (in centimeters) from baseline to the end of treatment. To evaluate the response to treatments, we assessed the changes in daily perception of pelvic pain, comparing the mean score recorded each month after device insertion with the mean score registered in the month before insertion.

Secondary outcomes were changes in the HRQoL that were evaluated using the EHP-30 questionnaire, which was administered at baseline and at 6 months after device placement. Furthermore, bleeding patterns were assessed from a menstrual calendar provided. Additionally, all participants recorded the intake of any pain medication, and all the adverse and serious adverse events were recorded and notified to the ethics committee, as required.

Statistical Analysis

The sample size was calculated on the basis of the noninferiority hypothesis of the ENG implant with respect to LNG-IUS. Several noninferiority studies using a VAS to measure pain have used a noninferiority margin of 1.5 cm. Gerlinger et al. (19) suggested a 1-cm noninferiority margin in endometrial-associated pelvic pain studies, recognizing that more studies were needed to come to this conclusion. A 1.5-cm noninferiority margin is considered and an SD of 2.5 cm. A minimum sample size of 45 women per study arm was needed, at 0.05 significance level and power equal to 0.80, to achieve noninferiority. Taking into account a dropout rate of 10%, 50 women should be included per study arm. The efficacy analyses were performed for the modified intention to treat analysis population, including all randomized women who had at least one efficacy evaluation. Missing data imputation was performed using last observation carried forward. The primary efficacy variable was evaluated using a 95% confidence intervals (CI). A linear model for repeated measures, with unstructured covariance parameters estimated by REML, was used to evaluate treatments outcome profiles, including the factor treatment and month. The HRQoL was evaluated by an analysis of variance model taking into consideration the two treatment groups and the two moments at which the EHP-30 questionnaire was applied. The SAS/STAT software program, version 9.4 was used (SAS Institute) (20).

RESULTS

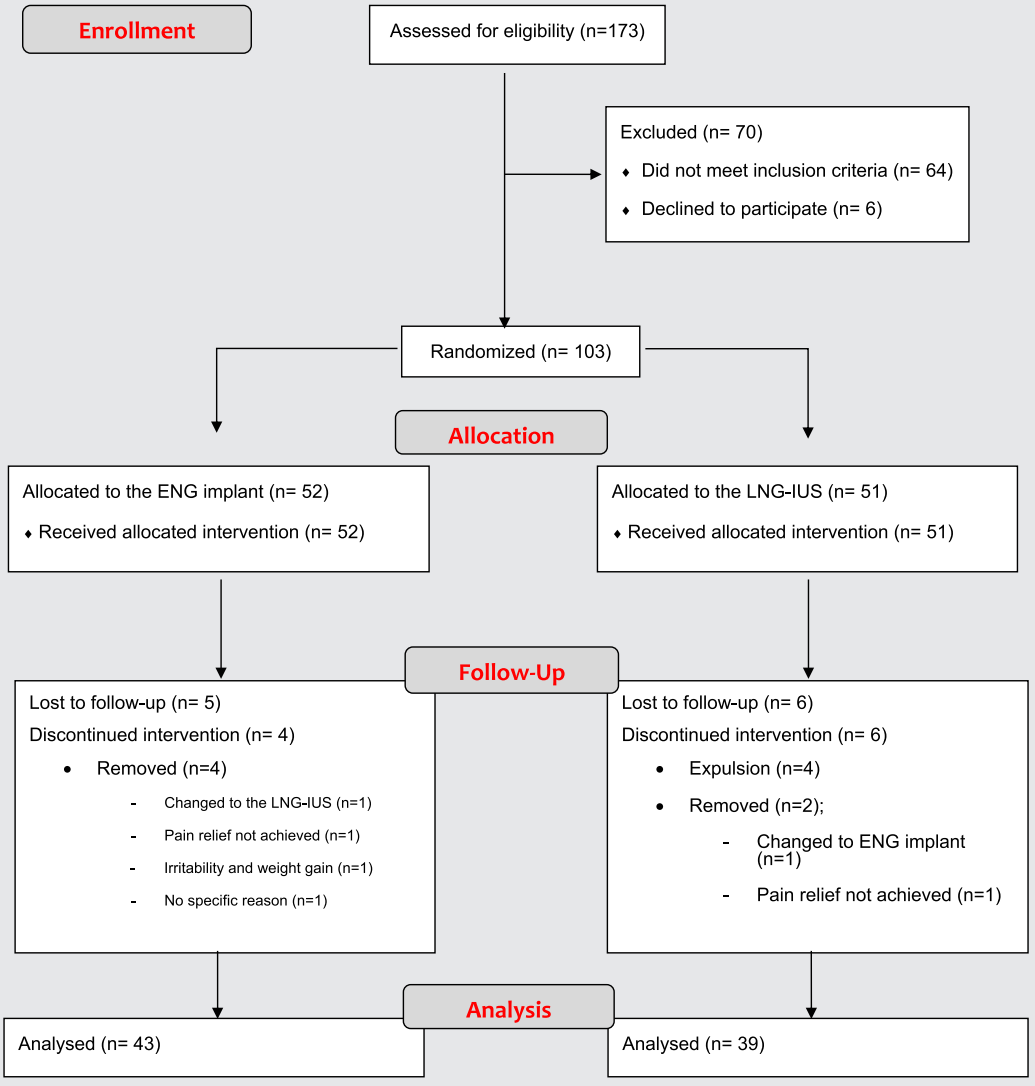
A total of 103 women met the inclusion criteria and agreed to participate in the study. They were then allocated to use either the ENG implant (n = 52) or the LNG-IUS (n = 51). A flowchart of the participants' admission to the study is shown in Figure 1. No adverse events occurred during insertion of the ENG implant or the LNG-IUS. The participants' sociodemographic characteristics are presented in Table 1. The two treatment groups were similar with respect to age, body mass index (kg/m^2), ethnicity, years of schooling, parity, and stage of endometriosis, as well as regarding the use of medications and drinking habits.

There was no significant difference between treatments for both endometriosis-associated noncyclic pelvic pain and dysmenorrhea mean changes from baseline to treatment end: 0.01 ± 0.72 (95% CI −1.10, 1.14). At 180 days of observation, VAS treatment noncyclic pain and dysmenorrhea profiles did not significantly differ (P=.241 and .431, respectively) when comparing ENG implant and LNG-IUS users. Furthermore, VAS noncyclic pelvic pain scores decreased significantly during the 180-day study period 5.6 ± 1.7 in 180 treatment days, from 7.6 ± 1.7 (95% CI 7.1, 8.0) to 2.0 ± 2.4 (95% CI 1.2, 2.7), among users of the ENG implant (mean difference, 5.6 ± 1.7; 95% CI −6.4, −4.7); and 5.5 ± 1.6 in 180 treatment days, from 7.4 ± 1.7 (95% CI 6.9, 7.9) to 1.9 ± 1.7 (95% CI 1.3, 2.4), among the LNG-IUS users (mean difference, 5.5 ± 1.6; 95% CI −6.2, −4.4) (P<.0001 for both groups).

In addition, VAS dysmenorrhea scores decreased significantly during the 180-day study period 5.3 ± 1.4 in 180 treatment days, from 7.5 ± 1.7 (95% CI 6.9, 8.1) to 2.2 ± 3.2 (95% CI 1.1, 3.2), among users of the ENG implant (mean difference, 5.3 ± 1.3; 95% CI −6.6, −4.3); and 5.4 ± 1.3 in 180 treatment days, from 7.3 ± 1.7 (95% CI 6.9, 7.9) to 1.9 ± 2.2 (95% CI 1.2, 2.7), among the LNG-IUS users (mean difference, 5.4 ± 1.3; 95% CI −6.3, −4.3) (P<.0001 for both groups). The most important reductions of noncyclic pelvic pain were observed at 30 and 60 days after device placement (−3.8 and −5.2 and −4.1 and −4.8 and among users of the ENG implant and the LNG-IUS, respectively). The main reductions of VAS score for dysmenorrhea were also observed at 30 and 60 days after device placement (−3.4 and −5.5 and −3.5 and −4.8 among users of the ENG implant and the LNG-IUS, respectively). After 60 days after placement of both devices VAS noncyclic pelvic pain and dysmenorrhea scores changes did not differ significantly through visits. The proportion of women who used pain killers before and through the intervention was similar in both groups of treatment. The HRQoL evaluation showed significant improvement in all the domains of the core and modular segments of the EHP-30 questionnaire in both treatment groups, with no significant differences between them (Table 2).

The most common bleeding patterns in the ENG implant users were infrequent bleeding (30.0%) and spotting (22.1%) in the first 90-day period and amenorrhea (28.8%) and infrequent bleeding (24.4%) at 180 days of follow-up. Regarding the LNG-IUS group, the most common bleeding patterns were spotting (36.1%) and prolonged bleeding (21.6%) in the first 90-day evaluation period and infrequent bleeding (30.0%) and spotting (22.1%) at 180 days of follow-up (Fig. 2).

FIGURE 1



Flowchart of participants: women screened for eligibility, admitted to and randomized in the study on the use of the ENG implant or the LNG-IUS for the treatment of endometriosis-associated pain, and reasons for noninclusion in analysis.

Carvalho. Endometriosis-associated pain control. Fertil Steril 2018.

DISCUSSION

Our findings indicated that the ENG implant is not inferior to the 52-mg LNG-IUS and that both devices are equally effective treatments for the control of endometriosis-associated noncyclic pelvic pain and dysmenorrhea and for the improvement of HRQoL during the first 6 months of treatment in women with endometriosis-associated pelvic pain. To the best of our knowledge, this is the first head-to-head RCT in which these two treatments are compared and the largest study to evaluate the effectiveness of the ENG implant for control of endometriosis-associated pelvic pain (6, 7).

Pain and infertility are probably the two consequences of endometriosis that most affect women with the disease and may be the greatest contributing factors to reduction of women's HRQoL. Not only was HRQoL found to be significantly lower in women with endometriosis, but pain intensity and the pain–cognition interaction were also identified as factors that affect HRQoL (21, 22).

Pain recurrence is common after conservative surgery for endometriosis, and the incidence of repeat surgery to resolve this symptom ranges from 13% to 40% (23). This fact motivated us to evaluate these two progestin-only contraceptives for that purpose, because both can be used for long periods and can be replaced at the end of their approved duration of use with only one small intervention for insertion every 3 or 5 years. Furthermore, these forms of treatment do not result in hypoestrogenism, which can also have a negative effect on HRQoL and limit the duration of use, and they offer not only pain relief and improvement of HRQoL but also provide highly effective contraception for those women who want to avoid a pregnancy.

TABLE 1

Selected characteristics of the participants.

Characteristic	Treatment group: ENG implant (n = 51)	Treatment group: LNG-IUS (n = 52)	*P* value
Age (y), mean ± SEM	33.4 ± 0.892	34.7 ± 0.925	.286
Body mass index (kg/m^2), mean ± SD	27.1 ± 0.752	27.8 ± 0.710	.546
Ethnicity			.595
White	42 (80.8)	39 (76.5)	
Other	10 (19.2)	12 (23.5)	
Years of schooling			.602
0–8	5 (9.6)	3 (5.9)	
9–11	28 (53.8)	32 (62.7)	
≥12	19 (36.6)	16 (31.4)	
Parity			.853
0	26 (50.0)	23 (45.1)	
1	13 (25.0)	13 (25.5)	
≥2	13 (25.0)	15 (29.4)	
ASRM classification			.654
Stage I + II	11 (21.2)	14 (27.4)	
Stages III + IV	18 (34.6)	14 (27.4)	
Deep endometriosis diagnosed at TVUS and MRI	23 (44.2)	23 (45.1)	

Note: Values are number (percentage) unless otherwise noted. ASRM = american society for reproductive medicine; MRI = magnetic resonance imaging; TVUS = transvaginal ultrasonography.

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An RCT compared the efficacy of the ENG implant with depot medroxyprogesterone acetate injection (DMPA) in reducing endometriosis-associated pain (7). In the same direction of our results regarding ENG implant users, the authors reported a 68% mean decrease in the VAS pain score after the first 6 months of use in the ENG implant group and 53% in the DMPA group (P=.36). At the beginning of the study, 18 of 21 and 20 of 20 women in the ENG implant group and the DMPA group, respectively, used analgesics; however, at the 12-month follow-up visit, the percentage of women using analgesics had decreased to almost 40%.

The ENG implant potentially represents a safe, new, effective, and convenient alternative treatment for endometriosis-associated noncyclic pelvic pain and dysmenorrhea and constitutes a valid option, particularly for the few women in whom insertion of the LNG-IUS fails owing to cervical stenosis (24) or for those who refuse to use any intrauterine device.

Two studies have evaluated the long-term effectiveness of the LNG-IUS in patients with endometriosis-associated pelvic pain (25, 26). Other authors (25) assessed the LNG-IUS for up to 30 months after insertion following surgical excision of endometriotic lesions and endometriomas. There was a significant decrease in the recurrence rate of dysmenorrhea (P=.019) and significant reduction in the mean dysmenorrhea VAS score when compared with

TABLE 2

EHP-30 results at baseline and at 180 d after device placement.

Parameter	ENG implant: Baseline (mean ± SD)	ENG implant: 180 d (mean ± SD)	ENG implant: *P* value	LNG-IUS: Baseline (mean ± SD)	LNG-IUS: 180 d (mean ± SD)	LNG-IUS: *P* value
Core questionnaire						
Pain	68.7 ± 13.2	38.2 ± 19.3	<.0001	65.2 ± 21.7	37.5 ± 17.7	<.0001
Lack of control or powerlessness	74.7 ± 16.3	42.2 ± 22.1	<.0001	66.9 ± 23.6	35.9 ± 19.1	<.0001
Emotional well being	71.6 ± 18.1	46.9 ± 20.0	<.0001	58.1 ± 21.3	43.1 ± 17.2	.0007
Social support	64.5 ± 23.9	42.9 ± 24.5	<.0001	55.1 ± 24.6	44.5 ± 22.2	.0284
Self-image	62.8 ± 24.4	41.9 ± 23.2	<.0001	50.3 ± 27.5	41.0 ± 26.2	.0462
Modular questionnaire						
Effect of endometriosis on:						
Work	41.2 ± 30.5	21.3 ± 19.9	.0002	38.8 ± 31.5	22.7 ± 20.3	.0012
Sexual intercourse	63.1 ± 29.9	38.9 ± 29.6	<.0001	63.5 ± 29.7	42.5 ± 23.6	.0004
Relationship with children	28.8 ± 34.7	18.1 ± 21.8	.0040	35.4 ± 34.6	21.8 ± 21.3	.0061
Feelings about the:						
Medical profession	39.7 ± 29.8	26.6 ± 19.2	.0082	43.1 ± 26.6	22.2 ± 14.7	<.0001
Treatment	55.0 ± 31.4	31.9 ± 17.5	<.0001	53.8 ± 28.0	30.3 ± 15.1	<.0001
Possibility of not conceiving	51.2 ± 35.7	31.7 ± 30.3	<.0001	36.7 ± 34.9	29.0 ± 28.8	.0837

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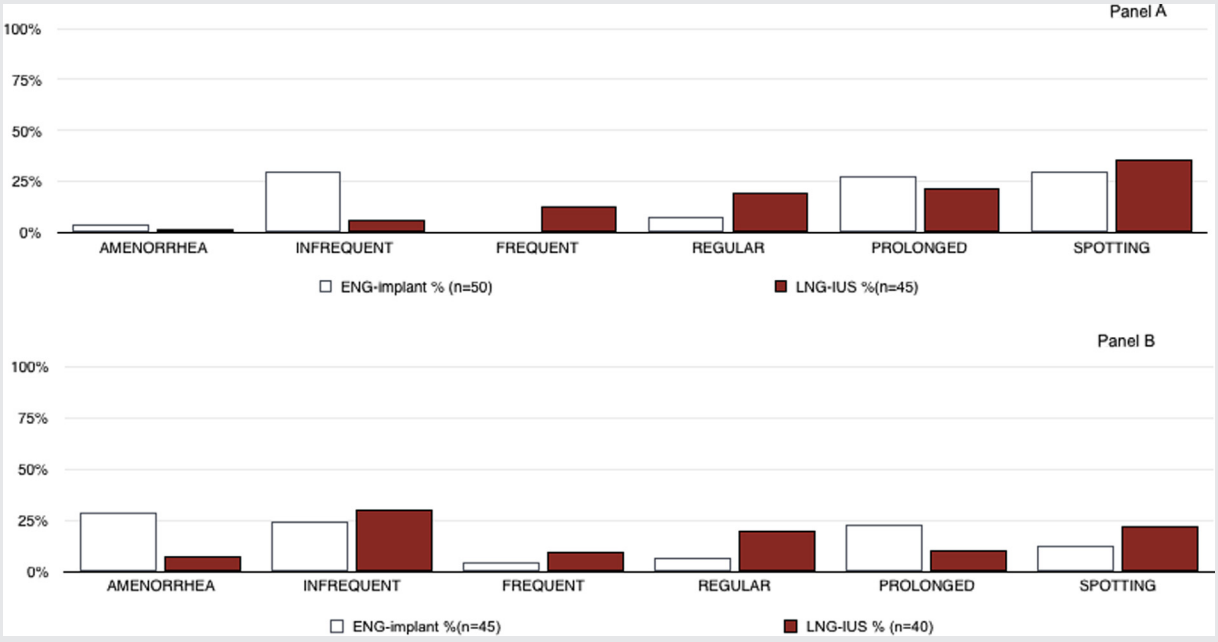
FIGURE 2



Bleeding patterns of LNG-IUS and ENG implant users in the first (**A**) and second (**B**) 90-day reference period.

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non-users. Additionally, a significant improvement in the VAS pain score (baseline 4.26 vs. 0.50, $P<.0001$) was reported among 28 patients after laparoscopic surgery for endometriosis followed up for 3 years after placement of the LNG-IUS (26).

The bleeding patterns reported in our study for both contraceptive methods are those commonly associated with progestin-only contraceptive use. In our study, amenorrhea was recorded in approximately 28.8 % and 10% of the ENG implant and the LNG-IUS users, respectively. None of the enrolled women had the implant or LNG-IUS removed because of bleeding disturbances disorders (27), possibly because women with endometriosis-associated pain are more prone to accept eventual bleeding disturbances because their main focus is pain control and the improvement of HRQoL. Furthermore, the findings of our study confirmed previous reports that endometriosis-associated pelvic pain exerts an important negative effect on HRQoL (4, 22).

The strengths of the study are the RCT design and the fact that almost 80% of the participants had a diagnosis of severe endometriosis, including deep endometriosis, which suggested that both treatments evaluated here can be recommended (28). However, the principal limitation of the study is the 10% loss to follow-up and the short duration of follow-up; therefore, results probably cannot be extrapolated for long-term treatment. Additionally, the lack of blinding could have introduced some bias; however, owing to the characteristics of both contraceptives it was not possible to have a blind study. Furthermore, the lack of a control/placebo group is also a limitation, although it is unethical to maintain women with endometriosis-associated pelvic pain on a placebo.

In conclusion, the study found no significant differences between the ENG subdermal contraceptive implant and the 52-mg 20-μg/d LNG-IUS in improving pelvic pain and dysmenorrhea and increasing HRQoL in women with endometriosis-associated pelvic pain and deep endometriosis. Both treatments are long-term feasible options for women with endometriosis-associated pelvic pain, with few side effects. Nevertheless, further studies are required, particularly with respect to the ENG implant, to enable the long-term effects of this treatment to be assessed in a larger sample.

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Control del dolor asociado a endometriosis con implante anticonceptivo liberador de etonogestrel y sistema intrauterino liberador de levonorgestrel de 52 mg: ensayo clínico aleatorizado

Objetivo: Evaluar la eficacia de un implante anticonceptivo de liberación de etonogestrel (ENG) o el sistema intrauterino de liberación de levonorgestrel (LNG-IUS) de 52 mg en el control del dolor pélvico asociado a endometriosis.

Diseño: Ensayo clínico aleatorizado de no-inferioridad en el que se asignó a mujeres con endometriosis el uso de un implante ENG (tratamiento experimental) o un LNG-IUS (comparador activo). Se realizaron visitas mensuales de seguimiento hasta los 6 meses.

Lugar: Hospital Universitario.

Pacientes: Ciento tres mujeres con dolor pélvico crónico asociado a endometriosis, dismenorrea, o ambos durante más de 6 meses. En casos de endometriosis profunda, se utilizaron como herramientas de diagnóstico adicionales la ecografía vaginal y la resonancia magnética.

Intervenciones: el implante de ENG o LNG-IUS se insertó en los primeros 5 días del ciclo menstrual.

Resultados principales: Niveles diario de dolor pélvico no cíclico y dismenorrea se evaluaron utilizando una escala analógica visual diaria. La calidad de vida relacionada a la salud se evaluó utilizando el cuestionario de perfil de salud de la endometriosis-30 al inicio del estudio y hasta por 6 meses. Los patrones de sangrado se evaluaron diariamente a partir de un calendario menstrual.

Resultados: Ambos anticonceptivos mejoraron significativamente la media de la escala visual análoga de la endometriosis asociada a dolor pélvico y dismenorrea sin diferencias significativas entre los perfiles de los grupos de tratamiento. La calidad de vida relacionada con la salud mejoró significativamente en todos los dominios de los segmentos centrales y modulares del cuestionario de perfil de salud de la endometriosis-30, sin diferencias entre ambos grupos de tratamiento. Los patrones de sangrado más comunes a los 180 días de seguimiento fueron la amenorrea y el sangrado infrecuente y el sangrado y manchado infrecuentes entre las usuarias de los implantes de ENG y LNG-IUS, respectivamente.

Conclusiones: En este estudio de no inferioridad, ambos anticonceptivos mejoraron significativamente el dolor pélvico, la dismenorrea y la calidad de vida relacionada a la salud en la endometriosis.