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ORIGINAL ARTICLE

The levonorgestrel-releasing intrauterine system is associated with a reduction in dysmenorrhoea and dyspareunia, a decrease in CA 125 levels, and an increase in quality of life in women with suspected endometriosis

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Background and aims: The aim of this study was to investigate the effectiveness of a levonorgestrel-releasing intrauterine device (LNG-IUS) in the symptomatic relief of pain in women with endometriosis and additionally, to assess the changes in women's life quality and serum cancer antigen (CA) 125 levels.

Materials and methods: All women who had an LNG-IUS inserted for the treatment of dysmenorrhea, chronic pelvic pain or both for more than six months over a two-year period were included in the study. Each woman was asked to complete questionnaires of the Short Form-36 and visual analogue scales (VAS) in the first visit and the third, sixth, ninth and twelfth months after the LNG-IUS insertion. CA 125 levels were measured at each visit.

Results: Forty-five women were included in the study. At the end of 12 months, mean dysmenorrhoea VAS score decreased from 6.13 to 2.88, mean dsyspareunia VAS score from 6.04 to 2.61 and CA 125 level from 50.67 to 22.45. Endometriomas reduced in size in six women (mean size decreased from 31 to 20 mm) and disappeared in three.

Conclusions: Several favourable outcomes were found following LNG-IUS insertion: (i) dyspareunia and dysmenorrhoea were clearly reduced; (ii) the size of endometriomas were decreased; (iii) CA 125 levels significantly decreased; (iv) a few women experienced the typical systemic adverse effects of progestogens; however, LNG-IUS-related adverse events were generally tolerable and the discontinuation rate was as low as 6.66% (3/45).

KEYWORDS

CA 125, contraception, endometriosis, levonorgestrel-releasing intrauterine device, life quality, Mirena

INTRODUCTION

Endometriosis is an inflammatory disease process, characterised by lesions of endometrial-like tissue outside the uterus that is associated with pelvic pain and/or infertility.[1] The most common symptoms are pelvic pain, menstrual and sexual dysfunction, infertility and pelvic masses (endometriomas). The goal of therapy is to relieve these symptoms. There is no high-quality evidence that one medical therapy is superior to another. Therefore, treatment decisions are individualised, taking into account the severity of symptoms, the extent and location of disease, whether there is a desire for pregnancy, patient's age, medication adverse effects, surgical complication rates and cost.

Nonsteroidal anti-inflammatory drugs, gonadotropin-releasing hormone analogues (GnRH-a), androgen derivatives, combined oral contraceptives and progestins are the most commonly used options in the treatment of endometriosis, most of which are associated with systemic adverse effects and this sometimes limits long-term use. New options such as the levonorgestrel-releasing intrauterine device (LNG-IUS) (Mirena, Bayer Schering Pharma, Leiras OY, Finland) are being investigated in the treatment of endometriosis because of the adverse effects associated with the currently available medical treatments.

The LNG-IUS provides an alternative for delivering the 19-c progestogen directly into the uterine cavity at a steady rate over a five-year period.[2,3] It is an option for empirical medical treatment of endometriosis prior to surgical diagnosis and treatment.[4] A recent Cochrane review demonstrated that LNG-IUS reduces the recurrence of painful periods in women with endometriosis.[5] Two previous trials including 95 women showed evidence of a significant decrease in recurrence of painful menstruation in the LNG-IUS group compared with the expectant management group (relative risk (RR) 0.22, 95% CI: 0.08–0.60).[6,7] In this study, our aim was to investigate the effectiveness of an LNG-IUS in the symptomatic relief of pain in women with endometriosis and additionally, to assess changes in women's life quality and serum cancer antigen (CA) 125 levels.

MATERIAL AND METHODS

This prospective, cross-sectional and non-comparative study was conducted in the Gynaecology Department of Istanbul Medeniyet University, Goztepe Training and Research Hospital Training and Research Hospital. Over a two-year period, consecutive women with suspected endometriosis who had moderate to severe dysmenorrhea, chronic pelvic pain or both for more than six months and were admitted for insertion of an LNG-IUS were included in the study. Women with these symptoms are considered to have endometriosis because it is the most frequent diagnosis; however, the diagnoses were not histopathologically confirmed and these women did not have any diagnostic surgery.

The inclusion criteria were: being aged 18–50 years; having regular menstrual periods (25–35 days intervals); no use of any hormonal therapy for ≥ 6 months prior to the study; and willing to use contraception. The exclusion criteria included: nondiagnosed vaginal bleeding; history of gynaecological cancer; having chronic diseases such as liver pathologies, diabetes mellitus or pelvic inflamatory disease; septic abortion history in the last three months; malignancy doubt in biopsies; fertility desire; uterus size larger than 10 weeks of gestational age; submucosal leiomyoma or polyp; breastfeeding; history of osteoporosis, coagulation disorders or allergy to progestins; and a history of hormonal medication use in the last three months.

Each woman gave informed consent at admission to the study and the institutional ethics committee also approved the study. Each woman was asked to complete questionnaires of the Short Form (SF)-36 health survey and visual analogue scales (VAS) in the first visit and the third, sixth, ninth and 12th months after LNG-IUS insertion. The SF-36 is a set of generic, coherent and easily administered quality-of-life measures that rely upon patient self-reporting. The VAS recorded non-cyclic pain, dysmenorrhoea, severity of effects of dyspareunia symptoms on life quality and degree of satisfaction after treatment.

After the gynaecologic anamneses were recorded, general physical and pelvic examinations were performed. A microorganism culture sample was taken if necessary and infections of the lower genital tract were treated with appropriate antibiotics. A routine Papanicolaou smear was performed. Uterus, adnexal areas and endometrium were all assessed using transvaginal ultrasound. Fourteen of the women had endometriomas on ultrasound and/or magnetic resonance imaging, so they were confirmed as having endometriosis. Diagnostic laparoscopy was not performed in the others; therefore, we do not have the exact diagnosis but considered them as having symptomatic endometriosis. When necessary, an endometrial biopsy was sampled using a Pipelle vacuum aspirator. Histologic assessment was performed in our hospital's pathology laboratories. CA 125 levels were also recorded. All women were re-examined in the first, third, sixth, ninth and 12th months. The LNG-IUS was checked using two-dimensional ultrasound and CA 125 levels were re-evaluated. VAS and SF-36 questionnaires were also re-evaluated.

Statistics

Statistical analysis was performed using the NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 (Statistical Software, East Kaysville, Utah, USA). Descriptive statistical methods (mean, standard deviation) were used in the evaluation of the study data. When comparing the quantitative data in the change analysis of the normally ranged parameters, the paired-samples *t*-test was used. For parameters other than that, the Wilcoxon signed-rank test was used. Qualitative data were specified as percentages. Intermittent variables were summarised as numbers and percentages, and constant variables were summarised as mean and minimum–maximum. Statistical significance was defined as $P < 0.05$.

RESULTS

In total, 45 women were included in the study. Two of them had noncyclic menorrhagia and pelvic pain, hence their LNG-IUSs were removed at the fourth and sixth months after insertion. One of them had mood swings and acne and her LNG-IUS was removed at the third month. The study was completed with 42 women at the end of 12 months.

The mean age was 36.77 ± 6.51 years (range, 23–48 years). The gravidae ranged from one to six with a median value of three. Twenty-eight (66.6%) women were smokers and there was a family history of endometriosis in 12 (28.57%) women.

When dysmenorrhoea VAS scores were compared with the before treatment scores, VAS scores of the third, sixth, ninth and 12th months showed a statistically significant decrease ($P < 0.01$; Table 1). With the exception of four, all women experienced a reduction in dysmenorrhoea pain score during the whole treatment period and none described an increase in pain.

Compared with the scores at the beginning of the study, there was a significant decrease in the third, sixth, ninth and 12th months dyspareunia VAS scores (Table 2). During the whole treatment period, the follow-up results for dyspareunia significantly decreased in 30 (71%) women in the first three months, 34 (80%) in the sixth month and 36 (85%) patients at the first year.

Before treatment, the mean CA 125 level of the study group was 50.67 ± 26.55 IU/mL, whereas by the end of the sixth month the CA 125 level was reduced to 32.72 ± 14.69 IU/mL, and 22.45 ± 10.23 IU/mL by the end of the 12th month. This decrease was statistically significant ($P < 0.01$).

At the beginning of the treatment period, 14 women had endometriomas with a mean size of 31.14 ± 12.59 mm (range, 20–34 mm). None of these cysts increased in size; lesions reduced in six patients (20.14 ± 8.43 mm) and disappeared completely in three patients.

Regarding the SF-36 health questionnaire, the calculated physical health scores increased from 43.42 ± 5.93 to 53.09 ± 6.86 by the end of 12 months. The mental health scores increased to 44.14 ± 5.12 from 38.14 ± 5.59. This effect was especially distinct in patients with a higher preliminary pain score.

TABLE 1 Dysmenorrhoea visual analogue scale scores in the treatment with a levonorgestrel-releasing intrauterine device

Treatment	Mean ± SD	Min–Max
Beginning	6.13 ± 1.15	4–8
Third month	3.73 ± 0.68	3–5
Sixth month	3.53 ± 1.01	1–5
Ninth month	3.12 ± 0.77	1–4
12th month	2.88 ± 0.74	1–4
Beginning – third month	**0.001***	
Beginning – sixth month	**0.001***	
Beginning – ninth month	**0.001***	
Beginning – 12th month	**0.001***	

*statistically significant

TABLE 2 Dyspareunia visual analogue scale (VAS) scores in the treatment with a levonorgestrel-releasing intrauterine device

Dyspareunia VAS Scores	Mean ± SD	Min–Max
Beginning	6.04 ± 0.95	4–8
Third month	4.22 ± 1.16	2–6
Sixth month	3.11 ± 0.95	1–5
Ninth month	2.97 ± 0.89	1–5
12th month	2.61 ± 0.82	1–4
Beginning – third month	**0.001***	
Beginning – sixth month	**0.001***	
Beginning – ninth month	**0.001***	
Beginning – 12th month	**0.001***	

*statistically significant

During the time period of LNG-IUS use, the most common adverse effect was a change in vaginal bleeding patterns. In the first three months, irregular menstruation and spotting were frequent, and at the end of the sixth and 12th months, amenorrhoea was the most common adverse effect. Other important adverse effects were pelvic pain seen in 13% of patients, headache (4.5%), mood swings (9%) and formation of new ovarian cysts (11%). The ovarian cystic lesions seen during treatment were simple follicular cysts < 3 cm in size, which disappeared or shrank spontaneously during follow-up.

At the end of the sixth month of treatment, 78% of women stated that they were satisfied with the treatment. At the end of year 1, patient satisfaction was reported as 83%. In the first six months of treatment (third, fourth and sixth months), LNG-IUSs were removed from three women because of adverse effects and these women were excluded from the study.

DISCUSSION

In the present prospective analysis, we investigated the efficacy of an LNG-IUS in a total of 45 women with suspected endometriosis in a single institution and found the following effects of LNG-IUS after one year: (i) dyspareunia and dysmenorrhoea were clearly reduced; (ii) the size of endometriomas were decreased; (iii) CA 125 levels significantly decreased; and (iv) a few persons experienced the typical systemic adverse effects of progestogens. However, LNG-IUS-related adverse events were generally tolerable and the discontinuation rate was as low as 6.66% (3/45).

One of the aims of our study was to find out whether endometrioma sizes change after the insertion of LNG-IUS. We had 14 women with endometriomas. At the end of one year, we saw that none of the cysts increased in size, the cysts reduced in size in six patients (mean size was 31.14 ± 12.59 mm and became 20.14 ± 8.43 mm) and disappeared completely in three patients. The second important finding of our study is that CA 125 levels significantly decreased after the treatment with LNG-IUS. Mean CA 125 level was 50.67 ± 26.55 IU/mL in the beginning and was reduced to 22.45 ± 10.23 at the end of one year.

The findings in our study are in agreement with previous studies, which showed rise in life quality standard[7–13] and pain relief[8,12,14,15] in women with endometriosis during use of LNG-IUS. Lockhat *et al.*[12] worked with 34 women with symptomatic endometriosis and they reported a reduction in pain symptom frequency and severity six months after LNG-IUS were applied. This research group also published three-year follow-up results of the same patients in 2005. The continuation rates of patients in the study were 85%, 68%, 62% and 56% at the sixth, 12th, 24th and 36th months, respectively. The most common reason for dropping out of the study was reported as irregular non-tolerable bleeding and noncyclic constant pain. The most frequent adverse effects were irregular bleeding (14.7%), unilateral abdominal pain (11.8%) and weight gain (8.8%).[16] In our study, the most common adverse effect was menstrual irregularities, which were especially prominent in the first six months, and amenorrhea. Twenty-four percent of women developed amenorrhea at the end of six months, and 44% were amenorrheic at the end of one year. One woman had her IUS removed due to pelvic pain, one due to mood swings, and one other due to headache and bleeding pattern changes in the first six months. During treatment, 18% of women had simple ovarian cysts up to 30 mm, which diminished spontaneously in three months. Minimal adverse effects were seen in many women but they were described as mild and tolerable. In our study, treatment satisfaction was 93.3% at the end of one year (three of 45 women wanted their IUD to be removed, the other 42 women were satisfied with the treatment). The adverse effects that these three women experienced were menorrhagia, pelvic pain, mood swings and acne.

Our study does have some limitations. The most important limitation is that there is no control group. The best trial method for future studies would be to randomise to LNG-IUS versus no intervention and to assess these same outcomes. The effectiveness of our treatment was expressed subjectively. SF-36 and VAS rely on patients' subjective perceptions and recall. The decrease in the size of endometriomas and the improvement in CA 125 levels can be used as objective parameters but none are related with pain severity. A VAS or verbal rating scale can be used for assessing pain. For life quality evaluation, other questionnaires exist; however, all are subjective methods in which patients evaluate themselves; therefore, they are all closely related to how the patient identifies and perceives pain.

CONCLUSION

Our study shows that LNG-IUS is associated with a reduction in dysmenorrhoea and dyspareunia-related pelvic pain, a decrease in CA 125 levels, and increase in life quality standards of women. The LNG-IUS has minimal systemic adverse effects and is generally well-tolerated. As such, it can be a good option for long-term hormonal therapy for women with dyspareunia and dysmenorrhoea.

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