CEOG Clinical and Experimental Obstetrics & Gynecology

Levonorgestrel-releasing intrauterine device use as an alternative to surgical therapy for uterine leiomyoma

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Summary

Objective: To evaluate the efficacy of the levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of leiomyoma related menorrhagia and to assess the effect of LNG-IUS on uterine, leiomyoma, and ovarian volume. *Materials and Methods:* In this prospective before and after study, LNG-IUS was inserted in 38 women with myoma-related menorrhagia. The patients were evaluated for serum levels of hemoglobin, hematocrit and uterine, leiomyoma, and ovarian volume at the time of insertion and at six months. *Results:* Significant reduction in the Pictorial Blood Loss Assessment Chart (PBAC) score and increases in serum hemoglobin levels and in amenorrhea was observed within three months. However, there was no statistically significant reduction in the myoma and uterine volume. Ovarian volume, also, did not changed significantly. *Conclusion:* The use of LNG-IUS is effective in reducing menorrhagia associated with leiomyomas with improvement in hemoglobin levels and may be a simple and effective alternative to surgical treatment of leiomyoma-related abnormal uterine bleeding (AUB-L) without significant influence on the volume of leiomyoma and ovarian and uterine volume.

Key words: Leiomyoma; Levonorgestrel; Intrauterine device; Menorrhagia.

Introduction

Uterine leiomyomas are the most common premenopausal benign uterine tumours, account for up to 40 percent of all hysterectomies in premenopausal women [1]. There are well established options for nonsurgical treatment include danazol, gonadotropin releasing hormone agonist (GnRH), uterine artery embolization, mifepristone (RU 486) [2]. However, their use is not widespread. Danazol is associated with marked androgenic side-effects and liver dysfunction [3]. GnRH analogues are expensive and associated with hypoestrogenism leading to hot flushes, vaginal dryness, and bone loss [4]. Uterine artery embolization has potential risks of premature ovarian failure and uterine synechia [5]. Compared to GnRH analogues, mifepristone is associated with less hypoestrogenic side effects. However, it was not found to reduce fibroid volume [6].

The levonorgestrel-releasing intrauterine system (LNG-IUS) is a widely used, highly effective contraceptive method [7]. In addition, there are many other non-contraceptive beneficial effects of LNG-IUS such as the reduction of excessive menstrual blood loss and therefore this system is now used for dysfunctional uterine bleeding [8]. Furthermore, the use of LNG-IUS has been considered specifically for the treatment of abnormal uterine bleeding (AUB) caused by leiomyoma, which is classified by the International Federation of Gynecology and Obstetrics (FIGO) as leiomyoma-related abnormal uterine bleeding (AUB-L) [9]. While LNG-IUS was shown to be effective in the management of AUB related to leiomyoma, studies concerning the effect of LNG-IUS on myoma size and uterine size have been published in recent years. Grigorieva *et al.* [10] reported that the use of LNG-IUS resulted in a reduction in myoma volume and total uterine volume. However, Maruo *et al.* [11] concluded that the use of levonorgestrel does not always lead to a reduction in the volume of leiomyomas and may even stimulate the proliferative potential of the leiomyoma cells. A recent study by Naki *et al.* has also supported findings of Maruo *et al.* [12]. Additionally, Inki *et al.* [13] suggested that LNG-IUS use in the treatment of menorrhagia is associated with the development of ovarian cysts. Therefore, the present study was designed to evaluate the effect of LNG-IUS on uterine volume, ovarian volume, and volume of leiomyomas.

Materials and Methods

This was a prospective before and after study. In total, 38 women of reproductive age (35-50 years) attending the present clinic because of menorrhagia associated with uterine myomas were enrolled into the study during 2009. Approval for the trial protocol and written informed consent of all patients were ob-

Revised manuscript accepted for publication November 19, 2013

tained. Size of the uterus estimated to be less than 12 weeks of gestation by pelvic and ultrasonographic examination and presence of one type II myoma (according to ESH) at least three cm in diameter or multiple myomas in which each one was greater than one cm in diameter measured by transvaginal ultrasonography were eligibility criteria.

Exclusion criteria were: 1) any concomitant medical disorder that may be a contraindication to LNG-IUS' use (e.g., congenital uterine anomaly, acute pelvic inflammatory disease (PID), abnormal cervical cytology, pregnancy); 2) type 0 or type I submucous myoma (European Society of Hysteroscopy classification); 3) myomas greater than five cm; 4) adenomyosis; 5) premalignant or malignant uterine and breast diseases; 6) use of oral contraceptives or oral progestagen during the previous three months; 7) the presence of an ovarian cyst or tumor.

Uterine bleeding was quantitatively assessed by a validated pad scoring method known as Pictorial Blood Loss Assessment Chart (PBAC). A PBAC score of 100 or more was considered to be a diagnostic of menorrhagia with a specificity and sensitivity of above 80% [14]. Complete physical, routine laboratory evaluation examination including hemoglobin, total leukocyte count, platelet count, thyroid profile, fasting blood sugar, transvaginal ultrasonography, and probe curettage was performed before insertion of LNG-IUS to exclude the possible underlying causes for hemorrhagia other than leiomyoma. The uterus, leiomyoma, and each ovary was measured in three dimensions and the uterine volume, the volume of the leiomyomas and ovarian volume was calculated using the formula for ellipsoid mass (4/3 x π x D1 x D2 x D3). In cases with multiple leiomyomas, total leiomyoma volume was calculated by the summation of each leiomyoma. Follicular cysts were not included in the calculation of ovarian volume. All transvaginal ultrasonography examination were performed with eight MHz probes by the same examiner, at the beginning of the study, also at the third and sixth months of LNG-IUS insertion. An IUS releasing 20 µg/day of levonorgestrel was inserted into the uterine cavity during days 5-7 of the menstrual cycle. Follow-up visits were scheduled at three and six months after insertion of the LNG-IUS. At these visits, the changes in bleeding pattern, assessed with the PBAC and hematocrit were considered. Additionaly, transvaginal sonography was carried out for evaluation of the uterine volume, volume of the leiomyomas, and ovarian volume. Absence of uterine bleeding for over three months was interpreted as amenorrhea, while infrequent uterine bleeding with intervals longer than 38 days were considered to be oligomenorrhea. The statistical analysis was done using statistical software (SPSS 10.0 for Windows) and Student's t-test, McNemar's test, and Friedman variance analysis were used, as appropriate. Significance level was defined as 0.05. Data were expressed as mean ± SD and percentage (%), where appropriate.

Results

Table 1 shows the clinical and sonographic characteristics of pretreatment and posttreatment. The mean age of the patients was 41.43 ± 4.859 years. An evaluation of the patients revealed significant increases in the serum levels of hemoglobin and hematocrit ($p < 0.05$ for each) and increase in amenorrhea incidence ($p < 0.01$, Table 2). After the third and sixth months, the PBAC score was reduced by 91.2% and 95.1%, respectively. Compared with preinsertion values, there were no statistically significant changes in uterine and ovarian volumes and the volumes of leiomyomas (Table 1). Unexpectedly, in 18 patients, increases in the volume of leiomyomas were observed. No early complications were observed following the insertion of the IUS.

Table 1. — *Levonorgestrel-releasing IUD effects on PBAC score, hemoglobin and hematocrit plasma levels, uterine volume, myoma volume, and ovarian volume (n=38).*

	Baseline	3rd month	6th month
PBAC score	410 ± 21	40 ± 17[b]	20 ± 3.0[a,b]
Hemoglobin, g/dl	10.7 ± 1.2	11.5 ± 0.9[b]	12.3 ± 0.8[a,b]
Hematocit, %	32.9 ± 3.0	35.3 ± 2.5[b]	36.9 ± 2.6[a,b]
Uterine volue, mm^3	487,818.6 ± 352,724.0	487,176.8 ± 353,724.6	485,962.8 ± 359,641.6
Myoma volume, mm^3	22,367.0± 21,879.1	22,025.5± 21,556.5	21,624.2 ± 21,090.6
Ovarian volume, mm^3	52,796,05 ± 45,093.173	52,744.74 ± 43,972.322	52,230.00 ± 43,414.368

Note: Data are shown as n (%) or mean ± SD.
[a] $p < 0.05$, compared with third month values.
[b] $p < 0.001$, compared with baseline scores.
[c] $p < 0.05$, compared with baseline scores.

Table 2. — *Baseline and LNG-IUS-related menstrual bleeding pattern of patients (n = 38).*

	Baseline	3rd month	6th month
Menorrhagia, % of the patients	100	65.8	23.7
Amenorrhea, % of the patients	0	23.7	52.6

Discussion

The present study confirmed that LNG-IUS is statistically effective in reducing PBAC scores and in increasing hemoglobin values in women with AUB-L. The impact of treatment in terms of PBAC scores and hemoglobin values was observed three months following insertion of the LNG-IUS. Furthermore, over half of the patients had amenorrhea by the end of this study. However, there was no reduction in the volume of the leioyomyomas and in the uterine volume. Even an increase in uterine fibroids volume was observed in 47% of the patients, at six months after the insertion of LNG-IUS. The present findings are in line with previous studies which the effectiveness of the LNG-IUS for reduction of menstrual blood loss in leiomyomas has been confirmed [10, 12, 13, 15-17, 18, 19]. Although LNG-IUS has proven its success in reducing bleeding, there has been much debate about the effect of LNG-IUS on leiomyoma and uterine volumes. Grigorieva *et al.* [10] demonstrated that LNG-IUS use among women with myomas resulted in a reduction in the volume of the myomas and in total uterine volume at 12 months. Size reduction, however, has not been consistent across studies listed in Table 3. In their study, Magalhes *et al.* [20], Socolov *et al.* [21] and Kriplani *et al.* [22] found that uterine volume had decreased

Table 3. — *Evidence for LNG-IUD use in patients with AUB-L.*

Author and year of publication	Number of cases with leiomyoma	Follow-up time	Hemoglobin	Menstrual blood loss	Uterine volume	Volume of the leiomyomas	Ovarian volume
Inki *et al.,* 2002 [13]	119	12 months	-	-	No change was observed	No change was observed	Association with the development of ovarian cysts
Grigorieva *et al.,* 2003 [10]	67	12 months	Increased[a]	PBAC score reduced[a]	Decreased[a]	Decreased[a]	-
Soysal *et al.,* 2005 [16]	32	12 months	Increased[a]	PBAC score reduced[a]	No change was observed	-	-
Magalhães *et al.,* 2007 [20]	27	36 months	-	-	Decreased[a]	No change was observed	-
Gunes *et al.,* 2008 [17]	21	12 months	Increased[a]	The mean number of pads used daily during menstruation decreased[a]	Decreased	-	-
Tasci *et al.,* 2009 [18]	25	12 months	Increased[a]	-	No change was observed	Decreased[a]	No change was observed
Naki *et al.,* 2010 [12]	60	6 months	Increased[a]	A decrease in VBS[*] score	No change was observed	Increased	-
Socolov *et al.,* 2011 [21]	96	12 months	-	PBAC score reduced[a]	Decreased[a]	No change was observed	-
Kriplani *et al.,* 2012 [22]	54	48 months	Increased[a]	PBAC score reduced[a]	Decreased[a]	Decrease	-
Xie *et al.,* 2012 [19]	29	12 months	Increased[a]	PBAC score reduced[a]	No change was observed	No change was observed	-
Present study, 2013	38	6 months	Increased[a]	PBAC score reduced[a]	No change was observed	No change was observed	No change was observed

[a:] $p < 0.05$, [*]VBS: Visual Bleeding Score.

significantly 12 months after insertion of LNG-IUS, whereas changes in leiomyoma volume were not significant. Considering the 30% natural growth rate per year of leiomyomas, it seems reasonable to suggest that LNG-IUS inhibits their growth [20]. The growth of leiomyomas rely on the ovary steroid hormone and is regulated by local growth factors. A research study found that after treatment with 25 mcg/ml LNG for 72 hours, in vitro, the IGF-1 mRNA level of fibroid cells was decreased remarkably, thus IGF-1 downregulation could induct cell growth inhibition and apoptosis on the uterine leiomyoma [23]. However, Naki *et al.* [12], demonstrated that leiomyomas increased by 23% at six months.

Studies evaluating the effects of LNG-IUS on ovarian function showed a weak relationship while LNG-IUS causes high levonorgestrel levels in endometrial tissue but low levels in the systemic circulation [18, 24]. However, LNG-IUS use in the treatment of AUB-L was found to be associated with the development of ovarian cysts at six months, but these were symptomless and showed a high rate (94%) of spontaneous resolution [13]. Few studies evaluated the effect of LNG-IUS use in AUB-L on ovarian function and volume and no significant change was found after 12 months follow up [13, 18]. Supporting this data, the present authors observed no significant change in ovarian volume at six months.

Twelve months follow up was suggested to reveal significant reduction in uterine and leiomyoma volumes [10, 18]. Therefore, lack of long-term follow up (> one year) is a recognized limitation of the present study, which otherwise might be beneficial in terms of a more accurate assessment of volumetric alterations related to insertion of LNG-IUS. However, it is proposed that three months follow up might be sufficient to observe a reduction in the incidence of bleeding disturbances [19].

In conclusion, the present study demonstrated that the use of LNG-IUS is effective in reducing menorrhagia associated with leiomyomas with improvement in hemoglobin levels and may be a simple and effective alternative to surgical treatment of AUB-L without significant influence on the volume of leiomyoma and ovarian and uterine volume. Additional trials are needed to define LNG-IUS' role in the treatment of symptomatic leiomyomas.

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