Taiwanese Journal of Obstetrics & Gynecology 54 (2015) 412–415

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Clinical experiences of the levonorgestrel-releasing intrauterine system in patients with large symptomatic adenomyosis

Dong Soo Park, Mi-La Kim*, Taejong Song, Bo Seong Yun, Mi Kyoung Kim, Hye Sun Jun, Seok Ju Seong

Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, CHA University, Seoul, South Korea

ARTICLE INFO

Article history:
Accepted 14 May 2014

Keywords:
adenomyosis
dysmenorrhea
heavy menstrual bleeding
levonorgestrel-releasing intrauterine system

ABSTRACT

Objective: The objective of this study was to evaluate the clinical aspects of the levonorgestrel-releasing intrauterine system (LNG-IUS) in patients with large adenomyosis associated with dysmenorrhea and/or heavy menstrual bleeding (HMB).

Materials and methods: Data were collected retrospectively from 48 patients with large adenomyosis (gestational age $\geq$ 12 weeks during pelvic examination) diagnosed via transvaginal ultrasonography between January 2008 and December 2009. Clinical outcomes, including symptomatic changes of dysmenorrhea and HMB, uterine volume change, complications, and the overall success rate were evaluated in each patient after treatment with the LNG-IUS.

Results: The patients' mean age was 41.7 ± 6.1 years, and the median follow-up duration was 20 months (range, 3–50 months). Significant improvements ($p < 0.01$) in dysmenorrhea and HMB were observed. There was no significant change in the uterine volume. The most common side effects were prolonged vaginal spotting ($n = 28$, 58.3%) and LNG-IUS expulsion ($n = 18$, 37.5%). Five (10.4%) patients underwent premature LNG-IUS removal and eight (16.7%) patients underwent hysterectomy. The overall success rate of the LNG-IUS was 68.8%.

Conclusion: The LNG-IUS is a suitable alternative treatment option for the management of dysmenorrhea and HMB prior to hysterectomy, for patients with large adenomyosis.

Introduction

Adenomyosis is a common gynecological disorder characterized by the presence of endometrial glands and/or stroma in the myometrium [1]. It is an important cause of dysmenorrhea and heavy menstrual bleeding (HMB), which occur in ~ 65% of women with adenomyosis and can result in a poor quality of life [2,3]. Traditionally, the diagnosis of adenomyosis was based on clinical findings and pathologic confirmation after hysterectomy. However, transvaginal ultrasonography (TVS) and magnetic resonance imaging have been shown to be accurate, noninvasive methods for diagnosis [3–6]. The development of such imaging techniques, significantly, offers women the options of medical and/or minimally invasive surgical treatments. The various medical treatment modalities for symptomatic adenomyosis include oral contraceptives, danazol, oral progestins, injectable progestins, gonadotropin-releasing hormone agonists, and the levonorgestrel-releasing intrauterine system (LNG-IUS). Minimally invasive surgical methods include uterine artery embolization, endometrial resection/ablation, and magnetic resonance-guided focused ultrasonography [6–10].

The noncontraceptive benefits of the LNG-IUS, particularly the effects on dysmenorrhea and HMB, have been proven to be effective against adenomyosis in many clinical trials; a significant decrease in dysmenorrhea and HMB in a majority of women was observed in five of these trials [2,3,11–13]. In a randomized comparison study, an enhancement in all aspects of the quality of life in hysterectomy patients was observed with the LNG-IUS during the 1-year follow-up [14]. However, there has been only one case report about the treatment of large symptomatic adenomyosis with the LNG-IUS [2]. Therefore, the objective of this study was to specifically evaluate the clinical aspects, including symptomatic

* Corresponding author. Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, CHA University, 566, Nonhyeon-ro, Gangnam-gu, Seoul 135-081, South Korea.
E-mail address: mila76@naver.com (M.-L. Kim).

http://dx.doi.org/10.1016/j.tjog.2014.05.009

changes, side effects, and the overall success rate, of the LNG-IUS in patients with large adenomyosis (gestational age ≥ 12 weeks during pelvic examination) associated with dysmenorrhea and/or HMB.

Materials and methods

A total of 48 premenopausal patients (27–53 years) participated in a retrospective study conducted from January 2008 to December 2009. The patients were diagnosed with adenomyosis using TVS and had a uterine size ≥ 12 gestational weeks during the pelvic examination along with symptoms of dysmenorrhea and/or HMB. All patients refused to undergo hysterectomy or use oral contraceptives, and provided informed consent for treatment of symptomatic adenomyosis with the LNG-IUS. This study was approved by the Institutional Review Board of CHA Gangnam Medical Center, CHA University, Seoul, Korea. The diagnostic criteria for adenomyosis with TVS had been reported in previous studies: globular and/or asymmetric thickening of the uterine wall, myometrial cysts, distorted and heterogeneous myometrial echotexture, focal or diffuse heterogeneous myometrial echotexture, a poorly defined endometrial–myometrial junction, and a poorly defined focus of abnormal myometrial echotexture [15,16]. The uterine volume was calculated using the formula for an ellipsoid (volume = 0.52 × length × anteroposterior diameter × transverse diameter).

The LNG-IUS was inserted into the uterine cavity during Days 5–7 of the menstrual cycle of all patients. After insertion of the LNG-IUS, we recommended follow-up visits every 3–6 months during the 1st year and every 6–12 months thereafter. Each follow-up visit typically entailed monitoring symptomatic changes of dysmenorrhea and/or HMB and TVS examinations to confirm the uterine volume and location of the LNG-IUS. Symptomatic changes were evaluated with a visual analog scale (VAS). Preinsertion symptoms of dysmenorrhea and HMB were assessed using a linear scale, with the left extreme defined as “no pain or no bleeding” (0 mm) and the right extreme defined as “worst pain or worst bleeding I have ever felt” (100 mm). The score itself was determined by measuring the distance from the left side of the scale to the point marked by patients as their level of pain and amount of menstrual blood. Any special events, such as an abrupt onset of bleeding or spontaneous LNG-IUS expulsion, were recorded as a complication or side effect. All follow-up data (i.e., symptomatic changes, side effects, and TVS findings) were retrospectively collected and analyzed.

Statistical analyses were performed using SPSS software for Windows version 20 (SPSS Inc., Chicago, IL, USA). The Shapiro–Wilk test was used to test the normality of the data. Descriptive data were expressed as the mean ± standard deviation. Skewed data were within the median and range. A Wilcoxon signed rank test was used to compare the subjective changes in symptoms and the uterine volume prior to and after the LNG-IUS insertion. Statistical significance was set at $p < 0.05$. All statistical tests were two-sided.

Results

During the study period, a total of 176 patients with dysmenorrhea and/or HMB were diagnosed with adenomyosis using TVS and treated with the LNG-IUS. Among these patients, 48 women showed a uterine volume ≥ 12 gestational weeks during the pelvic examination. The mean age of the 48 enrolled patients was 41.7 ± 6.1 years and the median follow-up duration was 20 months (3–50 months). The median uterine volume before the LNG-IUS insertion was 253.5 mL (range, 201–687 mL). The baseline characteristics and initial symptoms of the patients are listed in Table 1.

Table 1
Patients' baseline characteristics.

Characteristics	Mean ± SD or median (range), *n* (%)
Age (y)	41.7 ± 6.1
Gravidity	3 (0–7)
Parity	2 (0–3)
Body weight (kg)	57.8 ± 8.2
Height (cm)	159.6 ± 4.4
BMI (kg/m^2)	22.7 ± 3.0
Initial uterine volume (cm^3)	253.5 (201–687)
Follow-up duration (mo)	20 (3–50)
Initial symptoms	
Heavy menstrual bleeding (HMB), only	10 (20.8)
Dysmenorrhea, only	8 (16.7)
HMB + dysmenorrhea	30 (62.5)

SD = standard deviation.

Approximately 60% of the patients had both HMB and dysmenorrhea prior to the LNG-IUS insertion.

The mean VAS score for dysmenorrhea and HMB decreased after the LNG-IUS insertion. The mean symptom score for dysmenorrhea remarkably decreased from 5.81 ± 2.96 to 2.86 ± 2.8 after 3 months ($p < 0.01$); after 36 months, the mean symptom score decreased to 1.4 ± 1.65 ($p < 0.01$). The mean score for the subjective symptoms of HMB also decreased continuously similar to dysmenorrhea (from 6.94 ± 2.61 to 3.25 ± 3.02 after 3 months, $p < 0.01$; and to 0.89 ± 1.27 after 36 months, $p < 0.01$; Table 2).

The median uterine volume decreased from 253.5 mL to 232.5 mL after 6 months; after 36 months, it had increased to 267 mL. Nonetheless, these were no significant differences between the initial uterine volume and the volumes at 6 months and 36 months (Figure 1).

The most common side effect was abnormal uterine bleeding. Twenty-eight patients (58.3%) complained of prolonged vaginal spotting. Seventeen patients (35.4%) suffered from lower abdominal pain or lower back pain, and 17 patients (35.4%) reported watery discharge or foul odor from the vagina. However, these side effects were tolerable in most cases. Only three patients who complained of prolonged spotting and one patient who complained of abdominal pain requested the removal of the LNG-IUS.

Eighteen patients (37.5%) reported LNG-IUS expulsion. Most of the patients (11/18 patients) who experienced LNG-IUS expulsion wanted to reuse it because they had been satisfied with its clinical effects; however, four of these 11 patients experienced a second LNG-IUS expulsion. Seven of the 18 patients elected to discontinue using the LNG-IUS because they wanted to observe their symptoms without any interventions. Out of the four patients who experienced a second expulsion, one patient had the LNG-IUS reinserted and after that she did not experience a third expulsion during the follow-up periods. All expulsions occurred during the first 12 months, and most expulsions ($n = 15$) occurred during the first 6 months. There was no significant difference in the uterine volume between the expulsion [266.5 mL (201–687 mL)] and without expulsion [248.5 mL (201–384 mL)] groups ($p = 0.406$).

During the follow-up periods, 22 patients (45.8%) continued to use the LNG-IUS for treating adenomyosis. Five patients (10.4%) withdrew from treatment with the LNG-IUS owing to complications. Two patients (4.2%) had the LNG-IUS removed for a pregnancy trial, and one patient (2.1%) opted for LNG-IUS removal after menopause.

A total of eight patients (16.7%) underwent hysterectomy because of prolonged spotting ($n = 3$; 6.3%), repeated LNG-IUS expulsion ($n = 3$; 6.3%), severe abdominal pain ($n = 1$; 2.1%), and a lack of symptomatic improvement in HMB ($n = 1$; 2.1%).

Table 2
Subjective symptomatic change in dysmenorrhea and HMB before and after LNG-IUS insertion.

	Before insertion	After insertion				
		3 mo	6 mo	12 mo	24 mo	36 mo
No. of patients	48	36	17	31	15	9
Dysmenorrhea	58.1 ± 29.6	28.6 ± 28.0*	23.5 ± 20.3*	22.3 ± 25.9*	19.3 ± 19.8*	14.0 ± 16.5*
HMB	69.4 ± 26.1	32.5 ± 30.2*	25.3 ± 17.7*	25.2 ± 26.7*	18.7 ± 16.9*	8.9 ± 12.7*

Data are presented as mean ± SD.
* Significant difference relative to the before-insertion variables (Wilcoxon signed rank test; $p < 0.01$).
HMB = heavy menstrual bleeding; LNG-IUS = levonorgestrel-releasing intrauterine system; SD = standard deviation.

The overall LNG-IUS success rate among the 48 patients with large symptomatic adenomyosis was 68.8%; this group included patients who continued to use the LNG-IUS ($n = 22$), had the LNG-IUS reinserted after expulsion ($n = 8$), had the LNG-IUS removed for a pregnancy trial ($n = 2$), and had chosen to have the LNG-IUS removed after menopause ($n = 1$).

Discussion

Although the contraindications for intrauterine devices (IUDs; i.e., LNG-IUS) do not include uterine size, it is recommended that all IUDs be inserted in uteri at a depth of 6–9 cm [17]. The effectiveness of the LNG-IUS in patients with large symptomatic adenomyosis was established in this study during a median follow-up of 20 months (3–50 months). To the best of our knowledge, this is the first study to evaluate the effectiveness of the LNG-IUS in patients with large symptomatic adenomyosis, except for one case report [2]. Despite the large mean uterine volume in this study, we were able to show a significant symptomatic improvement in dysmenorrhea and HMB similar to previously reported findings [3,12,13]. Previously reported uterine volumes ranged from 113 mL to 156 mL [3,12,13], which is relatively small compared to the mean uterine volume recorded in this study (253.5 mL).

The efficacy of the LNG-IUS for reducing the uterine volume in cases of adenomyosis is controversial. Significant uterine volume reductions associated with the LNG-IUS were reported by Cho et al [12] and Sheng et al [13], but not by Bragheto et al [3]. In this study, there were no significant differences in uterine volumes; however, the volume trend changed from decreasing to increasing at 6 months after insertion, which is similar to the findings of Cho et al [12]. It is difficult to explain the observed changes in the volume trend. One possibility for this trend is the decline in the levonorgestrel concentration in the outer uterus. The local effects of the LNG-IUS might be sufficient to affect the endometrium, but might not be strong enough to affect the entire uterus. Bragheto et al [3], who used magnetic resonance imaging to monitor the effectiveness of the LNG-IUS for treating patients with adenomyosis, reported a significant reduction in the junctional-zone thickness without any significant reduction in the overall uterine volume. As expected, Bragheto et al [3] also observed an alleviation of pain and abnormal bleeding associated with adenomyosis.

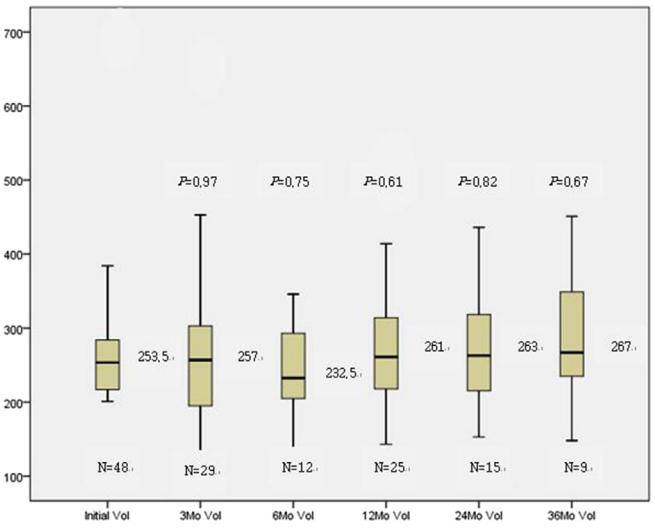

Figure 1. Changes in the median uterine volume before and after insertion of the levonorgestrel-releasing intrauterine system (LNG-IUS). Data were analyzed with the Wilcoxon signed rank test; no significant differences were observed between before and after LNG-IUS insertion.

The most common complication in this study was prolonged vaginal spotting ($n = 28$), which mostly occurred during the first 3 months ($n = 18$; 64.3%), and improved as time passed. Prolonged vaginal spotting might be associated with vessel density and/or vascular maturity of the endometrium. High concentration of levonorgestrel from the LNG-IUS is known to result in glandular atrophy and stromal decidualization. Therefore, during the early postinsertion period, these effects are combined with inflammatory changes associated with foreign body reactions, which aggravate apoptosis of the endometrial glands and stroma, and cause abnormal uterine bleeding [18–22]. Stephanie et al [23] reported that an endometrium exposed to the LNG-IUS for between 1 month and 3 months showed an 11.5-fold increase in small naked vessels, which are fragile. However, the vessel area and density increased dramatically in a time-dependent pattern after long-term treatment with the LNG-IUS. This vascular pattern change might explain the time-dependent improvement in patients with early abnormal uterine bleeding [23].

The LNG-IUS expulsion rate was as high as 37.5% in this study, which is much higher than previously reported values {Bragheto et al [3], 0% (0/29); Cho et al [12], 8.5% (4/47); Sheng et al [13], 16% (15/94)}. The high expulsion rate may be strongly associated with the large uterine volume observed in this study. According to several studies, the copper IUD expulsion rate was 2–8% during the 1st year after insertion [24–26]. Risk factors for IUD expulsion include young age, nulliparity, HMB, previous expulsion, and a uterine sounding depth > 9 cm [27–29]. Recently, Merki-Feld et al [30] reported that LNG-IUD expulsion was associated with parity, hysterometry, and a history of dislocations. The mean parity and hysterometry of their expulsion group were 2.4 cm and 8.6 cm, respectively [30]. In our study, all LNG-IUS expulsions occurred during the 1st year after insertion; the majority of expulsions occurred within 6 months and was usually associated HMB. These results are consistent with those previously reported [31,32]. Despite the high rate of expulsion in this study, 11 of 18 patients who experienced expulsion decided to have the LNG-IUS reinserted because of symptomatic improvement. Interestingly, although the median uterine volume of the expulsion group was greater than that in the without expulsion group, there was no significant difference in uterine volume [266.5 (201–687) mL vs. 248.5 (201–384 mL); $p = 0.406$].

This study had several limitations. First, this was a retrospective noncomparative study, and the follow-up periods among the patients were not equal, which made it difficult to perform comparisons. Accordingly, we used Wilcoxon signed rank tests (only 2 period comparisons) instead of the Friedman tests. A future prospective study is required to confirm our findings. Second, we evaluated the symptomatic changes of HMB using the VAS scale (usually used to assess pain intensity) prior to and after inserting the LNG-IUS rather than pictorial blood loss assessments or changes in the hemoglobin levels. In this study, the preinsertion hemoglobin levels were obtained from 35 of 48 patients, and 24 patients were diagnosed with iron deficiency anemia. Among them, only 13 patients were followed up and had their hemoglobin levels measured at 3–6 months. Although the hemoglobin levels were not available for all HMB patients, most of them experienced symptomatic improvement in the amount of menstrual blood loss without expulsion or removal of the LNG-IUS. Therefore, the symptomatic changes of HBM using the VAS scale were evaluated. Third, the sensitivity and specificity of TVS for diagnosing adenomyosis is 80–86% and 74–100%, respectively [16,33,34]. Fourth, the study populations in this study were too small for generalizing the results. The follow-up period of this study included only nine cases at 36 months and 15 cases at 24 months. This small sample size limited our ability to evaluate changes in the uterine volume in patients with large adenomyosis using the LNG-IUS. Despite these limitations, this was the first study to evaluate the LNG-IUS in patients with large symptomatic adenomyosis. A large-scale randomized study including comparisons with other conservative treatment methods and long-term follow-up data are required to confirm our results.

In conclusion, the LNG-IUS was a considerable treatment method for patients with large symptomatic adenomyosis. The LNG-IUS was observed to improve dysmenorrhea and HMB over time despite its high rate of expulsion.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

References

[1] Azziz R. Adenomyosis: current perspectives. Obstet Gynecol Clin North Am 1989;16:221–35.
[2] Fong YF, Singh K. Medical treatment of a grossly enlarged adenomyotic uterus with the levonorgestrel-releasing intrauterine system. Contraception 1999;60:173–5.
[3] Bragheto AM, Caserta N, Bahamondes L, Petta CA. Effectiveness of the levonorgestrel-releasing intrauterine system in the treatment of adenomyosis diagnosed and monitored by magnetic resonance imaging. Contraception 2007;76:195–9.
[4] Arnold LL, Ascher SM, Scruefer JJ, Simon JA. The nonsurgical diagnosis of adenomyosis. Obstet Gynecol 1995;86:461–5.
[5] Dueholm M, Lundorf E. Transvaginal ultrasound or MRI for diagnosis of adenomyosis. Curr Opin Obstet Gynecol 2007;19:505–12.
[6] Benagiano G, Brosens I, Carrara S. Adenomyosis: new knowledge is generating new treatment strategies. Womens Health 2009;5:297–311.
[7] Wood C. Surgical and medical treatment of adenomyosis. Hum Reprod Update 1998;4:323–36.
[8] Phillips DR. Endomyometrial resection of menopausal women with annoying uterine bleeding on estrogen replacement therapy. J Am Assoc Gynecol Laparosc 1995;2:19–24.
[9] Englander MJ. Uterine artery embolization for the treatment of adenomyosis. Semin Intervent Radiol 2008;25:387–93.
[10] Yoon SW, Kim KA, Cha SH, Kim YM, Lee C, Na YJ, et al. Successful use of magnetic resonance-guided focused ultrasound surgery to relieve symptoms in a patient with symptomatic focal adenomyosis. Fertil Steril 2008;90:2018.e13–5.
[11] Fedele L, Portuese A, Bianchi S, Dorta M, Raffaelli R. Treatment of adenomyosis-associated HMB with a levonorgestrel-releasing intrauterine device. Fertil Steril 1997;68:426–9.
[12] Cho S, Nam A, Kim H, Chay D, Park K, Cho DJ, et al. Clinical effects of the levonorgestrel-releasing intrauterine device in patients with adenomyosis. Am J Obstet Gynecol 2008;198:373–7.
[13] Sheng J, Zhang WY, Zhang JP, Lu D. The LNG-IUS study on adenomyosis: a 3-year follow-up study on the efficacy and side effects of the use of levonorgestrel intrauterine system for the treatment of dysmenorrhea associated with adenomyosis. Contraception 2009;79:189–93.
[14] Ozdegirmenci O, Kayikcioglu F, Akgul MA, Kaplan M, Karcaaltincaba M, Haberal A, et al. Comparison of levonorgestrel intrauterine system versus hysterectomy on efficacy and quality of life in patients with adenomyosis. Fertil Steril 2011;95:497–502.
[15] Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Sørensen JS, Olesen F. Magnetic resonance imaging and transvaginal ultrasonography for diagnosis of adenomyosis. Fertil Steril 2001;76:588–94.
[16] Reinhold C, Atri M, Mehio A, Zakarian R, Aldis AE, Bret PM. Diffuse uterine adenomyosis: morphologic criteria and diagnostic accuracy of endovaginal sonography. Radiology 1995;197:609–14.
[17] Nelson AL. Contraindications to IUD and IUS use. Contraception 2007;75:S76–81.
[18] Silverberg SG, Haukkamaa M, Arko H, Nilsson CG, Luukkainen T. Endometrial morphology during long-term use of levonorgestrel releasing intrauterine device. Int J Gynecol Pathol 1986;5:235–41.
[19] Luukkainen T, Lahteenmaki P, Toivonen J. Levonorgestrel-releasing intrauterine device. Ann Med 1990;22:85–90.
[20] Rogers PA, Au CL, Affandi B. Endometrial microvascular density during the normal menstrual cycle and following exposure to long-term levonorgestrel. Hum Reprod 1993;8:1396–404.
[21] Hickey M, Simbar M, Markham R, Young L, Manconi F, Russell P, et al. Changes in vascular basement membrane in the endometrium of Norplant users. Hum Reprod 1999;14:716–21.
[22] Jondet M, Letellier B, Verdys MT. Endometrial vascularization in levonorgestrel intrauterine device users; computerized microvessel measurement study. Contraception 2005;71:60–4.
[23] Stephanie R, Labied S, Blacher S, Frankenne F, Munaut C, Fridman V, et al. Endometrial vessel maturation in women exposed to levonorgestrel releasing intrauterine system for a short or prolonged period of time. Hum Reprod 2007;22:3084–91.
[24] Petta CA, Faundes D, Pimentel E, Diaz J, Bahamondes L. The use of vaginal ultrasound to identify copper T IUDs at high risk of expulsion. Contraception 1996;54:287–9.
[25] Rivera R, Chen-Mok M, McMullen S. Analysis of client characteristics that may affect early discontinuation of the TCu-380A IUD. Contraception 1999;60:155–60.
[26] Bahamondes L, Diaz J, Marchi NM, Petta CA, Cristofoletti ML, Gomez G. Performance of copper intrauterine devices when inserted after an expulsion. Hum Reprod 1995;10:2917–8.
[27] Thonneau P, Goulard H, Goyaux N. Risk factors for intrauterine device failure: a review. Contraception 2001;64:33–7.
[28] Castro A, Abarca L, Rios M. The clinical performance of the Multiload IUD: I. The influence of the endometrial cavity length. Adv Contracept 1993;9:285–90.
[29] Zhang J. Factors associated with copper T IUD removal for bleeding/pain: a multivariate analysis. Contraception 1993;48:13–21.
[30] Merki-Feld GS, Schwarz D, Imthurn B, Keller PJ. Partial and complete expulsion of the Multiload 375 IUD and the levonorgestrel-releasing IUD after correct insertion. Eur J Obstet Gynecol Reprod Biol 2008;137:92–6.
[31] Sivin I, Stern J, Coutinho E, Mattos CE, el Mahgoub S, Diaz S, et al. Prolonged intrauterine contraception: a seven-year randomized study of the levonorgestrel 20 mcg/day (LNg 20) and the Copper T380 Ag IUDs. Contraception 1991;44:473–80.
[32] UNDP/UNFPA/WHO/World Bank, Special Programme of Research, Development and Research Training in Human Reproduction: IUD Research Group. A randomized multicentre trial of the Multiload 375 and TCu380A IUDs in parous women: three-year results. Contraception 1994;49:543–9.
[33] Fedele L, Bianchi S, Dorta M, Arcaini L, Zanotti F, Carinelli S. Transvaginal ultrasonography in the diagnosis of diffuse adenomyosis. Fertil Steril 1992;58:94–7.
[34] Bazot M, Cortez A, Darai E, Rouger J, Chopier J, Antoine JM, et al. Ultrasonography compared with magnetic resonance imaging for the diagnosis of adenomyosis: correlation with histopathology. Hum Reprod 2001;16:2427–33.