Role of levonorgestrel-releasing intrauterine system in dysmenorrhea due to adenomyosis and the influence on ovarian function

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Summary

Background: The objective of this study was to evaluate the efficacy and side-effects of the levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of moderate or severe dysmenorrhea associated with adenomyosis and the influence on ovarian function. *Study Design:* The LNG-IUS was inserted into 60 women who had moderate or severe dysmenorrhea associated with adenomyosis diagnosed by transvaginal sonography. A visual analogue scale (VAS) of dysmenorrhea, uterine volume and serum-levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), etstradiol (E2), and prolactin (PRL) were used to assess the efficacy of the treatment at baseline and at six and 12 months after the LNG-IUS. Serum-levels of FSH, LH, E2, and PRL were tested in pre-and post-insertion at six and at 12 months, respectively. Side-effects were recorded at every follow-up visit. *Results:* After six and 12 months of LNG-IUS insertion, dysmenorrhea was obviously alleviated, and the dysmenorrhea scores decreased to 2.6 from 0.6 ($p < 0.05$). The volume of uterus reduced six months after insertion and later, but without significant change ($p < 0.05$). After treatment of serum, in terms of FSH, LH, and E2 levels, compared with pre-insertion, there was no statistically significant difference ($p > 0.01$). However, the level of PRL markedly declined at six and 12 months after LNG-IUS. *Conclusion:* The LNG-IUS appears to be an effective method in alleviating dysmenorrhea associated with adenomyosis with little effect on ovarian function. It may be helpful to decrease the level of PRL in these patients.

Key words: Adenomyosis; Dysmenorrhea; Levonorgestrel-releasing intrauterine system.

Introduction

Adenomyosis is a common disorder that affects more than five percent of women in their reproductive age [1] and is one of the most common causes of dysmenorrhea. Women suffering from moderate or severe dysmenorrhea are often under mental stress before their expected menses. Until recently, the only definitive means of diagnosing and curing adenomyosis was hysterectomy [2, 3]. The recent development of non-surgical diagnostic techniques, such as transvaginal sonography (TVS) and magnetic resonance imaging (MRI), makes it possible for gynecologists to investigate conservative treatment to manage dysmenorrhea associated with adenomyosis [4, 5]. The levonorgestrel-releasing intrauterine system (LNG-IUS) was initially devised for contraception. It releases 20 mcg/day of LNG into the uterine cavity for a five-year period [6]. Besides the high contraceptive efficacy of the LNG-IUS, it has been demonstrated that the device also benefits women in other aspects, such as symptoms control with endometriosis and adenomyosis [7-11]. Compared with the studies on the efficacy in the treatment of dysmenorrhea, there has been limited literature regarding the influence of ovarian function after LNG-IUS insertion. The objective of this study was to evaluate the efficacy, side-effects, the influence on ovarian function, and acceptability of the LNG-IUS in the treatment of moderate or severe dysmenorrhea associated with adenomyosis.

Materials and Methods

Sixty women aged between 30 and 45 years with complaints of moderate or severe dysmenorrhea were recruited to participate in this study, This study was conducted in accordance with the declaration of Helsinki and with the approval from the Ethics Committee of Xinjiang Obstetrics and Gynecology Hospital. Written informed consent was also obtained from all participants.

Adenomyosis was diagnosed by TVS exam according to the criteria described by Dueholm *et al.* [5]. Patients were excluded if they had any of the following conditions: hormonal therapy in the preceding three months, immediate desire to conceive, chronic pelvic inflammatory disease, contraindications to progestins or contraindications to the use of an intrauterine contraceptive device. The symptom intensity was assessed by a 100-mm visual analogue scale (VAS), in which 0 indicated no pain and 100 indicated an unbearable pain. The severity of dysmenorrhea was graded as follows: a score of 1-50 was considered mild pain, 51-80 was considered moderate pain, and 81-100 was considered severe pain [7]. Once a woman met the inclusion criteria, she was requested to complete VAS scoring of dysmenorrhea. Her uterine volume, serum FSH, LH, E2, and PRL levels and menstrual pattern were recorded as the baseline variables before the LUG-IUS insertion. The uterine volume was calculated by using the formula

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Table 1 – *The efficacy of LNG-IUS against pain M (P25, P75) after placement for six months.*

Time	Dysmenorrhea VAS score	Dysmenorrhea VRS score	Dyspareunia VAS score	Dyspareunia VRS score	Chronic pelvic pain VAS score
Before placing	8.5 (6.5,10.0)	2.0 (1.0,3.0)	0.0 (0.0,2.0)	0.0 (0.0,1.0)	0.0 (0.0,3.0)
6 months after placing	2.0 (0.0,3.0)	1.0 (0.0,1.0)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.0 (0.0,0.0)
Z value	-6.613	-6.240	-3.508	-3.231	-3.846
p value	0.0002	0.003	0.0006	0.0008	0.0002

Table 2 – *The efficacy of LNG-IUS against pain M (P25, P75) after placement for 12 months.*

Time	Dysmenorrhea VAS score	Dysmenorrhea VRS score	Dyspareunia VAS score	Dyspareunia VRS score	Chronic pelvic pain VAS score
Before placing	8.5 (6.5,10.0)	2.0 (1.0,3.0)	0.0 (0.0,2.0)	0.0 (0.0,1.0)	0.0 (0.0,3.0)
12 months after placing	0.0 (0.0,1.0)	0.0 (0.0,1.0)	0.0 (0.0,0.0)	0.0 (0.0,0.0)	0.0 (0.0,0.0)
Z value	-6.692	-6.438	-3.509	-3.231	-3.993
p value	0.0003	0.0002	0.0006	0.0008	0.0008

Table 3 – *The efficacy of LNG-IUS on sex hormone levels after placement for six months regarding adenomyosis.*

Time	FSH (mIU/ml)	LH (mIU/ml)	E2(mmol/l)	PRL (ng/ml)
Before insertion	8.07±1.59	8.87±1.67	95.02±29.01	22.11±10.09
Follow-up after 6 months	7.84±1.44	8.55±1.52	103.07±24.92	18.11±7.20
t value	1.535	1.146	1.149	4.496
p value	0.249	0.061	0.471	0.001

Table 4 – *The efficacy of LNG-IUS on sex hormone levels after placing for 12 months regarding adenomyosis.*

Time	FSH (mIU/ml)	LH (mIU/ml)	E2 (mmol/l)	PRL(ng/ml)
Before insertion	8.07±1.59	8.87±1.67	95.02±29.01	22.11±10.09
Follow-up after 12 months	7.67±1.23	8.43±1.17	104.35±24.90	19.45±5.73
t value	1.457	1.134	1.134	4.483
p value	0.240	0.057	0.396	0.001

for an ovoid: volume = $D_1 \times D_2 \times D_3 \times 0.52$. The LNG-IUS was then inserted into her uterine cavity during menses on cycle day 5-7 by a senior gynecologist. The LNG-IUS was composed of a T-shaped polyethylene core surrounded by a reservoir of 52 mg of LNG, which was delivered to the endometrium at a release rate of 20 mcg/day in a sustained fashion for five years. The women underwent follow-up visits at three,six, and at 12 months after the LNG-IUS insertion. At each follow-up visit, a TVS was performed, a serum FSH, LH, E2, and PRL test was done and the VAS exams were performed by the same physician. Menstrual patterns before and after three, six, and 12 months of the LNG-IUS insertion were assessed and classified as normal, absent bleeding, infrequent bleeding, light regular bleeding, light prolonged regular bleeding, heavy regular bleeding or irregular bleeding [12]. Additionally, side-effects were also recorded at every visit. At the 12th month's visit, the women were requested to rate her overall degree of satisfaction with the treatment as follows: very satisfied, satisfied, uncertain, dissatisfied or very dissatisfied [7]. The VAS score of dysmenorrhea before and after the LNG-IUS insertion were compared by using the Wilcoxon signed rank test. The paired T test was used to compare the variables of uterine volume and serum FSH, LH, E2, and PRL levels before and after the LNG-IUS insertion.

In this study, data processing was conducted by means of SPSS 15.0 statistical analysis software, the data presenting normal distribution took the form of ± s, and those showing non-normal distribution adopted the form of M (P25, P75). T test was used to deal with those measurement data in line with the normal distribution, and Wilcoxon signed rank test, $\alpha = 0.05$ was used to handle those data with non-normal distribution.

Results

Pain Score

After the LNG-IUS insertion, dysmenorrhea, painful intercourse, chronic pelvic pain, dysmenorrhea VAS score, and sexual VRS pain score were significantly decreased (Tables 1 and 2). Among them, after inserting LNG-IUS for six months, there were 21 cases of disappearance of dysmenorrhea with patients (35.00%, 21/60), and 11 cases with sexual pain in patients with complete remission (68.75%, 11/16). At follow-up 12 months later, there were 17 cases with dysmenorrhea disappeared, corresponding to 28.33% (17/60).

Measured results of reproductive hormone serum levels

Before LNG-IUS insertion and after LNG-IUS insertion for six and 12 months, in terms of serum FSH, LH, and E2 levels in 60 patients, there were no statistically significant differences ($p > 0.05$), whereas the PRL level was significantly lower than preoperative levels ($p < 0.05$, Tables 3 and 4).

Renewal rate of patients after 12 months insertion

In the 12th month of follow-up, with the exception of one patient demanding to remove the ring, the other patients expressed their willingness to continue to use LNG-IUS, with a renewal rate of 98.33%. The former case patient was aged

46 years and demanded to remove the ring due to her menopause for seven months since the insertion of LNG-IUS. After the removal of the ring, her menopause continued with no recurrence of pain.

Discussion

This study shows promising effectiveness of using the LNG-IUS in alleviating adenomyosis-associated dysmenorrhea during a period of three years. The efficacy was observed throughout the three-year follow-up period, along with the reduction of uterine volume and serum PRL levels. The most remarkable changes in pain relief were observed at three and six months post-insertion, which were consistent with the results reported previously [11, 13]. Although the changes after six months were not as remarkable as those within the first six months, the authors must emphasize that the changes were constant and continuous, and the lowest VAS score was obtained at 36 months. In this study, the authors also found some side- effects reported by a small proportion of the women, which were the main reasons for premature removals. The discontinuation rate was 34% at three years, similar to that reported by a LNG-IUS study on endometriosis [14]. Albeit there were some side-effects, they were acceptable in comparison with the severe pain that those women previously experienced. The present study shows that 72.5% of women were very satisfied with the treatment at 12 months. Overall, the treatment has a high satisfaction rate. Since this was a conservative therapy, the authors could not prove the disappearance of the adenomyotic lesions, but the reduction of uterine volume and serum CA125 levels might reflect the shrinkage of the foci after the LNG-IUS insertion. Furthermore they also found shrinkage of adenomyoma and disappearance of some classic adnomyosis image by TVS in some women after the LNG-IUS insertion. In the present study, albeit there was a slight increase in uterine volume after 12 months of treatment, the difference was not significant compared with the volume at 12 months.

The mechanism of pain control action of the LNG-IUS in adenomyosis is unclear. It may correlate with serum levels of LNG or with the local concentration of LNG on the endometium or with the combination of these two. The relatively high levels of serum LNG during the first months on the device (459.2 - 357.3 pg/ml) [15] may explain the dramatic improvements after the LNG-IUS insertion in a short period of time. The local mechanism may be the effect of high concentration of LNG on the eutopic endometrium, which results in glandular atrophy and stromal deciduation. A similar effect may also occur on the ectopic endometrium, which results in glandular atrophy and stromal deciduation. A similar effect may also occur on the ectopic endometrium, resulting in an endometrial inactivity to the estrogen in circulation via down-regulation of estrogen receptors [16]. In addition, the endometrial inactivity may decrease the production of prostaglandin I2, a substance that can cause pain and uterine contraction, resulting in pain relief [17]. Another local mechanism has been proposed: that the direct effect of the progestin on the junctional zone leads to a reduction in the invasion and progression of myometrial hypertrophy [13].

The significant value of the present study showed that after the use of LNG-IUS, the patients remained in ovulatory cycle, and it had little impact on ovarian function. Serum levels of reproductive hormones measured results show that in terms of FSH, LH, and E2, before and after the use of the LNG-IUS in patients with adenomyosis, there were no significant differences, however, the PRL level was significantly lower than the pre-placement of LNG-IUS. E2 levels in blood reflecting the ovarian function is the most direct evidence of impaired ovarian function, due to a reduction in the level of ovarian hormone secretion, the decline in performance for E2, but the rise of FSH and LH. The rise of FSH and LH is caused by the fact that the decrease in ovarian secretion of estrogen increases its role in the pituitary due to the negative feedback; while FSH and LH levels increase, it can inhibit follicle development and ovum development, so that ovarian function recesses and the generation of E2 further is reduced. As a result, monitoring the level of FSH and LH may be a more accurate assessment of ovarian function. Therefore, the blood FSH, LH, and E2 values of these 60 cases in this group were determined on the third day of menstrual cycle. The results showed that: for all patients, before and after placement of LNG-IUS for six and 12 months, there were no significant differences in FSH, LH, and E2 levels ($p > 0.05$), the placing of intrauterine LNG-IUS for the treatment of adenomyosis does not affect the patient's ovarian function. After the use of LNG-IUS, the ovarian secretion of E2 remains normal and FSH and LH do not increase, without any effect upon reproductive health. The study also showed that with LNG-IUS placement, the PRL levels with patients can be reduced, or return to normal levels. The decline in PRL levels will be beneficial for patients to recover to normal pituitary gonadotropin secretion, to promote normal ovarian function and normal ovulation, and to regain normal corpus luteum function. Accordingly, patients are liable to return to normal menstruation and infertility patients have easier access to fertilization.

The relatively high expulsion rate in the present study may be due to enlargement of the patients' uteri and distortion of the uterine cavities, resulting from adenomyosis and adenomyoma, which may increase the possibility of the device descending or expelling. Another possible reason for expulsion is heavy regular bleeding, which causes the device to be expelled. In the present study, the most common reason for premature removals was irregular bleeding followed by lower abdominal pain.

In the present study, the most common side-effect appeared to be weight gain. Since the authors did not have a control group and the mean age of the women was 36.8 ± 4.3 years, there was a possibility that this weight gain might be a reflection of changes that often occur in the general

community in this particular age group of women. Similar amounts of weight gain occur with the copper and LNG-IUS. Therefore, the authors cannot conclude that this weight gain is caused by the LNG-IUS. The incidence rate of other side-effects, such as breast tenderness, skin problems, and headaches, which may be related to the LNG in the circulation [18], is not higher than that of other medical treatments including danazol, continuous combined oral contraceptives and depot medroxyprogesterone [19]. The incidence of ovarian cyst formation is similar to that reported in a previous study [20]. Women with ovarian cysts were asymptomatic and had a high rate of spontaneous resolution. Despite the side-effects of this procedure, the women in this study showed a steady increase of satisfaction rate with a corresponding decrease of dissatisfaction rate along the 12 months treatment period, partly due to the alleviation of dysmenorrhea. In this study, women who had previously used analgesics such as NSAAIDs and some Chinese traditional medicine no longer required their use or needed to use them only in very small doses after the LNG-IUS insertion.

This study has some limitations. First, it was not a multicenter, randomized, comparative study. Second, the diagnostic criterion of TVS for adenomyosis in the study had a sensitivity varying between 68% and 89% and a specificity between 65% and 99% [4, 21-23]. Third, overall satisfaction degree rating by the patients was used instead of a quality-of-life analysis to assess the overall effectiveness of the treatment.

In conclusion, the present study indicates that the LNG-IUS shows effectiveness in pain relief over a long period of time in women suffering from adenomyosis. Despite some side-effects, this treatment modality shows to be promising, with a high patient's satisfaction rate on the increase over the 12 month treatment period. It also has little effect on ovarian function, as compared with other drugs. It also has a higher value of compliance and application and may be a valuable long-term alternative for the treatment of adenomyosis.

References

[1] Azziz R.: "Adenomyosis: current perspectives". *Obstet. Gynecol. Clin. North Am.,* 1989, *16,* 221.

[2] Wood C.: "Surgical and medical treatment of adenomyosis". *Hum. Reprod. Update,* 1998, *4,* 323.

[3] Ferenczy A.: "Patophysiology of adenomyosis". *Hum. Reprod. Update,* 1998, *4,* 312.

[4] Uduwela A.S., Perea M.A., Aiqing L., Fraser I.S.: "Endometrial-myometrial interface: relationship to adenmyosis and changes in pegnancy". *Obstet. Gynecol. Surv.,* 2009, *55,* 390.

[5] Dueholm M., Lundorf E., Hansen E.S., Ledertoug S., Serensen J.S., Olesen F.: "Magnetic resonance imaging and transvaginal ultrasonography for diagnosis of adenomyosis". *Fertil. Steril.,* 2001, *76,* 588.

[6] Luukkainen T., Lahteenmaki P., Toivonen J.: "levonorgestrel-releasing intrauterine device". *Ann. Med.,* 1990, *22,* 85.

[7] Vercellinni P., Aimi G., Paonazza S., Degiorgi O., Pesole A., Crosignani P.G.: "A levnorgestrel-releasing intrauterine systerm for the treatment of dysmenorrhea associated with endometriosis: a pilot study". *Fertil. Steril.,* 1999, *72,* 505.

[8] Vercellini P., Frontiono G., DE Giorgi O., Aimi G., Zaina B., Crosignani P.G.: "Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study". *Fertil. Steril.,* 2003, *80,* 305.

[9] Lockhat F.B., Emembolu J.O., Konje J.C.: "The evaluation of the effectiveness of an intrauterine-administered progestogen(levonorgestrel) in the symptomatic treatment of endometriosis and in the staging of the disease". *Hum. Reprod.,* 2004, *19,* 179.

[10] Fedele L., Bianchi S., Raffaelli R., Portuese A., Dorta M.: "treatment of adenomyosis-associated menorrhagia with a evonorgestrel-releasing intrauterine device". *Fertil. Steril.,* 1997, *68,* 426.

[11] Fong Y.F., Singh K.: "Medical treatment of a grossly enlarged adenomyotic uterus with the levonorgestrel-releasing intrauterine system". *Contraception,* 1999, *60,* 173.

[12] Fraser I.S., Critchley H.O., Munro M.G., Broder M.: "A process designed to lead to international agreement on terminologies and definitions used to describe abnormalities of uterine bleeding". *Fertil. Steril.,* 2007, *87,* 466.

[13] Bragheto A.M., Caseta N., Bahamondes L., Petta C.A.: "Effectiveness of the levonorgestrel-releasing intruaterine system in the treatment of adenomyosis adenomyosis diagnosed and monitored by magnetic resonance imaging". *Contraception,* 2007, *76,* 195.

[14] Lockhat F.B., Emembolu J.O., Konje J.C.: "The efficacy, side-effects and continuation rates in women with symptomatic endometriosis undergoing treatment with an intra-uterine administered progestogen(levonorgestrel): a 3-year follow-up". *Hum. Reprod.,* 2005, *20,* 789.

[15] Lochhat F.B., Emembolu J.E., Konje J.: "Serum and peritoneal fluid levels of levonorgestrel in women with endometriosis who were treated with an intrauterine contraceptive device containing levonorgestrel". *Fertil. Steril.,* 2008, *83,* 398.

[16] Hurskainen R., Salmi A., Paavonen J., Teperi J., Rutanen E.: "Expression of sex steriod receptors and ki-67 in the endometria of menorrhagic women:effect of intrauterine levonorgestrel". *Mol. Hum. Reprod.,* 2000, *6,* 1013.

[17] MCGavigan C.J., Dockery P., Metaxa-mariatou V., Campbell D., Stewart CJ., Cameron I.T. et al.: "Hormonally mediated disturbance of angiogenesis in the human endometrium after exposure to intrauterine levonorgestrel". *Hum. Reprod.,* 2003, *18,* 77.

[18] Gardner F.J., Konje J.C., Abrams K.R., Brown L.J., Khanna S., Al-Azzawi F. et al.: "Endometrial protection from tamoxifen-stimulated changes by a levonorgestrel-releasing intrauterine system:a randomised controlled trial". *Lancet,* 2000, *356,* 1711.

[19] Vercellini P., De Giorgi O., Oldani S., Cortesi I., Panazza S., Crosignani P.G.: "Depot medroxyprogesterone acetate versus an oral contraceptive combined with very-low-dose danazol for long-term treatment of pelvic pain associated with endometriosis". *Am. J. Obstet. Gynecol.,* 1996, *175,* 396.

[20] Inki P., Hurskainen R., Palo P., Ekholm E., Grenman S., Kivelä A. et al.: "Comparison of ovarian cyst formation in women using the levonorgestrel-releasing intrauterine system vs. hysterectomy". *Ultrasound Obstet. Gynecol.,* 2002, *20,* 381.

[21] Bazot M., Cortez A., Darai E., Rouger J., Chopier J., Antoine J.M. et al.: "Utrasonography compared with magnetic resonance imaging for the diagnosis of adenomyosis of adenomyosis:correlation with histopathology". *Hum. Reprod.,* 2001, *16,* 2427.

[22] Atzori E., Tronci C., Sionis L.: "Transvaginal ultrasound in the diagnosis of diffuse adenomyosis". *Gynecol. Obstet. Invest.,* 2006, *42,* 39.

[23] Fedele L., Bianchi S., Dorta M., Zanotti F., Brioschi D., Carinelli S.: "Transvaginal ultrasonography in the differential diagnosis of adenomyoma versus leiomyoma". *Am. J. Obstet. Gynecol.,* 1992, *167,* 603.

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