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Original Article

Postoperative maintenance levonorgestrel-releasing intrauterine system for symptomatic uterine adenomyoma

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ABSTRACT

Objective: To evaluate whether a maintenance levonorgestrel-releasing intrauterine system is effective for preventing the recurrence of postoperative adenomyosis-related symptoms.
Materials and methods: From January 2005 through December 2014, a retrospective study including 133 patients with symptomatic adenomyosis undergoing conservative uterine-sparing surgery followed by gonadotropin-releasing hormone agonist treatment was conducted. We excluded the 18 patients who did not meet the inclusion criteria. The patients of intervention group (n = 54) received a levonorgestrel-releasing intrauterine system (LNG-IUS), which was inserted after surgery. The patients without LNG-IUS insertion were enrolled in the control group (n = 61). The primary outcome was improvement of adenomyosis-related dysmenorrhea, which was evaluated by the visual analog scale (VAS) and by hemoglobin (Hgb) and CA-125 levels.
Results: Over a 12-month follow-up, the intervention group exhibited a greater reduction in dysmenorrhea as assessed with a VAS score (mean ± SD: 6.5 ± 2.5 vs 4.1 ± 3.6, $p = 0.001$) and a greater elevation in the Hgb level (2.1 ± 1.9 vs 1.0 ± 1.7, $p = 0.008$) than the control group. At the end of the 24-month follow-up period, the intervention group also exhibited a greater reduction in dysmenorrhea as assessed with a VAS score (mean ± SD 6.1 ± 2.7 vs 3.7 ± 3.7, $p = 0.002$) and a greater elevation in the Hgb level (1.9 ± 2.1 vs 0.7 ± 1.8, $p = 0.022$) than the control group. The CA-125 level was significantly lower in the intervention group during the postoperative follow up (12th month follow-up, intervention vs control, 24.5 ± 28.8 vs 50.1 ± 44.0, $p = 0.005$; 24th month follow-up, 28.6 ± 26.2 vs 75.4 ± 68.5, $p = 0.002$).
Conclusion: The maintenance therapy of LNG-IUS is effective and well accepted for long-term therapy after conservative surgery for patients with adenomyosis.

Introduction

Uterine adenomyosis is a gynecological disorder characterized by invasion of endometrial tissue into the myometrium [1] with related symptoms, mostly dysmenorrhea, heavy menstrual bleeding, chronic pelvic pain, and dyspareunia [2]. Currently, the diagnosis of adenomyosis is based on pathological findings, which are characterized by the presence of heterotopic endometrial glands and stroma within the myometrium, 2.5 mm in depth or more than one microscopic field at 10 times magnification from the endometrium–myometrium junction, or the thickening of the junction equal to 12 mm or greater [3,4].

Hysterectomy is the "gold standard" treatment for adenomyosis, as Fedele et al. noted that it is not possible to isolate the adenomyotic tissue adequately [5]. For childbearing women who desire to preserve their uterus, medical treatment is usually the

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first-line therapy. Alternatively, if the patient cannot tolerate the side effects of long-term medical treatment or if the disease is refractory to medical intervention, conservative uterine sparing surgery may be an option for those women. Conservative uterine-sparing surgery can be classified as complete excision of adenomyosis for focal adenomyoma, cytoreductive surgery (partial adenomyomectomy) for diffuse adenomyosis, and non-excisional techniques [6]. Conservative surgery may not completely clear adenomyoma, as it occasionally involves the whole uterus diffusely (adenomyosis), and separating normal myometrial tissue from myometrial tissue invaded by adenomyoma can be difficult [7].

Due to the transient effect of medical therapy, and the low (50%) effectiveness of conservative uterine-sparing surgery in managing uterine adenomyoma-related symptoms, a combination of conservative surgery and medical treatment either with a gonadotropin releasing hormone (GnRH) agonist or with danazol has been developed. In a non-randomized prospective study [8], Wang et al. demonstrated that the symptom-relapse rates for the combination treatment of conservative surgery and GnRH agonist were statistically significantly lower than those with surgery alone (28.1% vs. 49.0%, respectively) at the end of the 2-year follow-up period. Liu et al. also supported that surgical-medical treatment provides an effective treatment option for the dysmenorrhea of adenomyoma [9]. Furthermore, combination of conservative surgery and a GnRH agonist also provides effective symptom relief and better reproductive performance in subfertile women with uterine adenomyosis than in women who received GnRH agonist alone [10].

The medical treatment of adenomyosis follows the principle of the management of endometriosis, which is aimed at reducing endogenous estrogen production and inducing endometrium differentiation, includes GnRH agonists, progestin, danazol, oral contraceptives, selective estrogen receptor modulators (SERM), selective progesterone receptor modulators (SPRM), aromatase inhibitors or a levonorgestrel-releasing intrauterine system (LNG-IUS) [11,12]. GnRH agonists and LNG-IUS have been proven to be better for symptom control in adenomyosis than other hormonal treatment [11,12]. However, GnRH agonists cannot be applied for long-course treatment due to side effects such as hot flashes, genital atrophy and osteoporosis. Additionally, adenomyosis-associated symptoms usually return after the cessation of postoperative hormonal therapy. Therefore, maintenance therapy for postoperative adenomyosis is a reasonable approach for prolonging the recurrence-free period.

Levonorgestrel-releasing intrauterine system (Mirena, Bayer Ag, Turku, Finland) is a suitable medical device for maintenance therapy because it directly delivers 20 μg/d of levonorgestrel into the uterine cavity over its 5-year life span. It has been proven to be more effective in alleviating dysmenorrhea and heavy menstrual bleeding associate with adenomyosis than hysterectomy [13–15]. Moreover, our previous study demonstrated that maintenance LNG-IUS therapy after surgery resulted in greater reductions in dysmenorrhea, non-cyclic pelvic pain and cancer antigen 125 (CA-125) levels in patients with ovarian endometrioma than in those without LNG-IUS in a 30-month follow-up [16].

The objective of our study was to examine the efficacy of LNG-IUS maintenance therapy after conservative uterine-sparing surgery for preventing the recurrence of adenomyosis-related symptoms.

Materials and methods

A total 133 patients with symptomatic adenomyosis (ranging from 28 to 52 years old) that received uterine-sparing surgeries were enrolled in this retrospective study from January 2005 to December 2014 from a single medical center (Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taiwan). Pre-operative evaluation included history taking, pelvic examination, complete blood count, blood biochemistry, serum CA-125 workup, and transvaginal or transabdominal ultrasonography examination. Ultimately, the women scheduled for elective conservative uterine sparing surgery were included in the study. All the patients enrolled for screening were the consecutive cases of one study surgeon (Y.J. Chen). The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taiwan, R.O.C. (VGH IRB: 960402).

Patients were included if they had histologically proven adenomyosis or adenomyoma, received uterine-sparing surgery and received postoperative GnRH agonist therapy. Patients who received less than three months of GnRH agonist therapy, had LNG-IUS insertion more than six months after the operation, or had medical diseases such as chronic renal failure and malignancy were excluded.

All patients received postoperative GnRH agonist treatment for three to six months in two forms [3.75 mg leuprorelin acetate i.m. (Leuplin® depot; Takeda Pharmaceuticals, Osaka, Japan) once every 4 weeks for 3–6 doses or Triptorelin pamoate 11.25 mg (Diphereline P.R.® 11.25 mg; Ipsen Pharma Biotech, Signes, France) once every 12 weeks for 1–2 doses]. The first doses of the two medications were injected within three days after the operation. Before the surgery, we explained the therapeutic and side effects of LNG-IUS to the patients, and after considering their fertility demand and preference, the patients decided whether to insert the LNG-IUS.

Participants

Seventy patients who received only conservative uterine sparing surgery and GnRH agonist treatment (without LNG-IUS inserted) were included in the control group. In the intervention group, 63 patients received a GnRH agonist and maintenance LNG-IUS treatment after conservative uterine sparing surgery (Fig. 1).

The collected baseline information included age, parity, body mass index (calculated as weight (kg)/height $(m)^2$), and the severity of dysmenorrhea. Dysmenorrhea was measured using a linear visual analog scale (VAS) [17]. The VAS consisted of a nongraduated 10-cm line ranging from “no pain” to “pain that is as bad as it could be”. The score was measured using a ruler with a minimum measuring unit of 1 cm and was obtained from the regular OPD visiting.

Surgical technique

The surgery was performed by laparotomy or laparoscopy. All surgeries were performed under general anesthesia.

Uterine-sparing surgeries for adenomyoma can be divided into adenomyomectomy for focal adenomyosis and cytoreductive surgery for extensive adenomyosis [18]. For focal adenomyomectomy, we separated the normal myometrium and adenomyoma, and the lesion was excised. Cytoreductive surgery for diffuse adenomyosis requires the massive removal of adenomyotic foci including a large amount of healthy myometrium, and the technique is similar to uterine myomectomy either by laparotomy or by laparoscopy [18,19].

The laparotomy included careful and thorough recognition of the adenomyotic foci in the uterus. Before uterine wall incision, vasopressin (20 IU/ml in 80 ml normal saline) was locally injected to the lesion to reduce blood loss during surgery. We incised the uterine wall along the adenomyoma, which could be vertical or a wedge resection of the uterus [6,18,20]. Then, the lesion was dissected with scissors, knife, and/or diathermy. After the lesion was excised, the endometrial cavity was sutured with absorbable

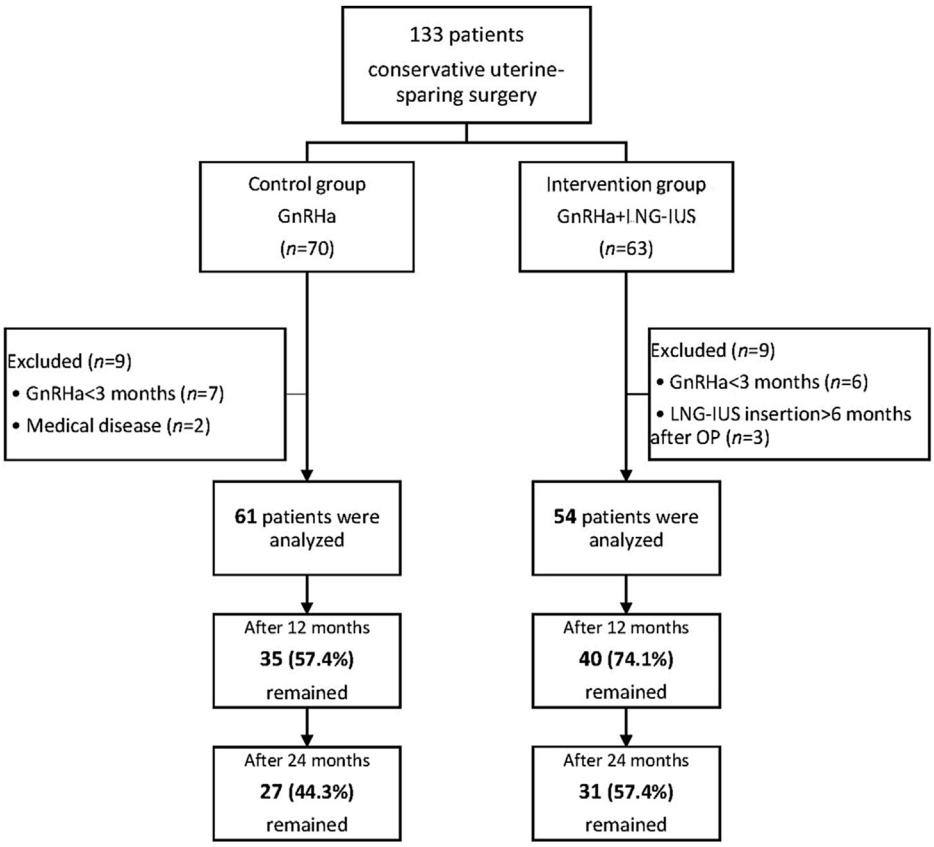

Fig. 1. The flow chart of group allocation and follow up.

suture when necessary, and the uterine defect was closed with multilayer suturing similar to that in myomectomy. The adenomyotic tissue was removed, leaving myometrium 1 cm from the serosa and from the endometrium [6,18,20].

In the laparoscopy procedure, the patients were placed in the lithotomy position, and the uterine manipulator (K-UMI, Thomas Medical Inc., Indianapolis, USA) was inserted into the uterine cavity. After establishing the pneumoperitoneum, observing the abdominal cavity, and carefully inspecting the location and the border of adenomyosis, we infused dilute vasopressin into the adenomyotic tissue directly and made a longitudinal or transverse incision of the uterine serosa with monopolar diathermy along the lesion. The resection of the adenomyoma was performed using scissors and monopolar and/or bipolar diathermy similar to the laparotomy [19,21]. The endometrial cavity and uterine wall were closed with absorbable suture (Vicryl®; Ethicon, Somerville, NJ, USA) or a knotless tissue closure device (Quill™ SRS; Angiotech Pharmaceuticals, Vancouver, BC, Canada) in one or two layers. The resected mass was removed directly in laparotomy cases, and in laparoscopy cases, it was put into a single-use retrieval bag (Endobag™, Covidien, Dublin, Ireland) and removed via an umbilical wound extended to approximately 2–2.5 cm.

In the intervention group, a LNG-IUS was inserted into the uterine cavity by the surgeon while the patient was still unconscious under general anesthesia [16]. Specimens were sent for histopathological evaluation to confirm the presence of adenomyosis or adenomyoma in all patients.

Follow-up

The follow up procedure was acquired from the outpatient department records from January 2005 to May 2017. Follow-up visits occurred every 6 months after treatment. After the patients had met with a gynecologist, ultrasonography and treatment were provided as indicated. The hemoglobin (Hgb) and serum CA-125 levels at the 12th and 24th month after the operation were recorded. The dysmenorrhea VAS score was evaluated at the operation and at the 12th and 24th month after the operation.

The statistical analysis was performed using IBM SPSS Statistic Viewer Ver.22 (IBM Corp., Armonk, NY, USA). The general characteristics were analyzed by Student's t-test for continuous data and χ^2 square for categorical data. The Hgb and CA-125 levels and dysmenorrhea VAS were compared by Student's t-test, and p-value < 0.05 was considered statistically significant.

Results

A flow chart of study participant selection was provided in Fig. 1. Initial evaluation identified 133 patients who received conservative uterine sparing surgery with histopathological tissue samples confirming the diagnoses of adenomyosis or adenomyoma. All patients had dysmenorrhea. However, 13 patients had GnRH agonist therapy less than three months, three patients had the LNG-IUS insertion more than six months after surgery, one had chronic kidney disease under hemodialysis, and one had Hodgkin lymphoma; all were excluded. Ultimately, 115 patients satisfied the eligibility criteria. Of these, 54 patients were analyzed in the intervention group, and 61 patients were analyzed in the control group. For the patients who received conservative uterine sparing surgery for adenomyomectomy, most were focal type adenomyosis, which appeared as a localized, intra-myometrial mass. In our study, most of the large adenomyomas were over the posterior wall and accounted for 28 in the control group (48.3%) and 33 in the intervention group (66.7%).

The baseline characteristics of the population are provided in Table 1. The two groups were comparable in terms of age, obstetric history, body mass index, uterine size and CA-125. However, preoperative dysmenorrhea VAS scores were significantly higher in the intervention group (control vs intervention: 6.9 ± 3.4 vs 8.6 ± 1.6, $p = 0.006$). Baseline Hgb levels were significantly lower in the intervention group (control vs intervention: 11.7 ± 2.1 vs 10.8 ± 2.3 mg/dL, $p = 0.037$) (Table 2).

At 12 and 24 months, the CA-125 level reduced significantly in the intervention group compared to the control group (Table 2). At 12 and 24 months after surgery, the VAS score for dysmenorrhea exhibited greater reductions in the intervention group than in the control group, and the Hgb levels were also significantly elevated in the intervention group compared to the control group (Table 3).

The pregnancy outcome is shown in Table 4. In the control group, four patients had full-term live birth delivery, while three patients experienced missed abortion. Two patients in the intervention group delivered live infants after removal of the device at 14 months and 24 months, including one patient with uterine rupture who underwent emergency cesarean section.

Discussion

Compared to conservative uterine surgery followed by GnRH agonist therapy only, the maintenance LNG-IUS therapy had more favorable improvements in hemoglobin levels, dysmenorrhea VAS and serum CA-125 levels at follow up at 12 and 24-months. This study suggested that the postoperative maintenance LNG-IUS therapy was effective for preventing adenomyosis-related symptom relapse. According to the literature review, there is no previous study that evaluated the maintenance LNG-IUS therapeutic effects for patients with adenomyosis after conservative uterine sparing surgery.

In our study, maintenance LNG-IUS significantly reduced dysmenorrhea VAS score at 12 and 24 months after surgery. The LNG-IUS could improve the dysmenorrhea by downregulating the estrogen receptors, causing ectopic foci to reduce in size, and resulting in decreased prostaglandin production [11,22]. Zhang et al. evaluated 21 patients with enlarged adenomyosis who underwent three or four months of GnRH agonist appliance and LNG-IUS insertion. After 12 months of implantation, the dysmenorrhea VAS decreased from 93.7 ± 0.2 to 58.2 ± 11.5, and shrinkage of uterine volume was noted [23]. In our study, the decrease of dysmenorrhea VAS was more profound than that seen by Zhang et al., which may due to the impact of combination with uterine-sparing surgery.

In Wang et al.'s study, the Hgb level was 12.1 ± 1.6 at 12 months after adenomyomectomy followed by GnRH agonist therapy [8]. In our control group, the Hgb level was normal after conservative uterine-sparing surgery and GnRH agonist treatment. However, the Hgb level exhibited greater improvement after maintenance LNG-IUS at 12 and 24 months. The possible reason is that the LNG-IUS might decrease the menstrual blood flow by causing decidualization of the endometrium and allowing the uterus to contract more efficiently due to the size reduction of adenomyotic foci [11,22,23].

The CA-125 level in adenomyosis is possibly correlated with disease severity because the CA-125 level in an endometriosis patient correlates with the endometriosis stage, lesion size and adhesion score [24]. According to a retrospective study by Al Jama et al. [10], adenomyomectomy followed by 6 months of GnRH agonist therapy resulted in decreased CA-125 after 12 months

Table 1
Basic characteristics of control and intervention groups.

	Control group $n = 61$	Intervention group $n = 54$	p
Age (year)	38.5 ± 5.3	38.8 ± 5.1	0.767
BMI (kg/m^2)	22.2 ± 3.6	23.4 ± 5.1	0.187
Gravida = 0 (%)	33 (54.1)	22 (40.7)	0.116
≥1 (%)	28 (45.9)	32 (59.3)	.
Parity = 0 (%)	44 (72.1)	27 (50.0)	0.015[a]
≥1 (%)	17 (27.9)	27 (50.0)	.
Presence with leiomyoma (%)	34 (55.7)	26 (48.1)	0.416
Presence with endometrioma (%)	11 (18.0)	6 (11.1)	0.297
Uterine size before surgery (cm^3)	191.6 ± 144.7	247.9 ± 171.7	0.059
Adenomyosis Type			1.0
Diffuse	3	3	.
Focal	58	51	.
Location of largest adenomyoma			0.121
Anterior wall (%)	18 (31.0)	12 (23.5)	
Posterior wall (%)	28 (48.3)	34 (66.7)	
Fundal wall (%)	12 (20.7)	5 (9.8)	
Operation Type			0.238
Laparotomy myomectomy (%)	17 (27.9)	10 (18.5)	
Laparoscopic myomectomy (%)	44 (72.1)	44 (81.5)	.
Operation time (min)	174.5 ± 62.6	167.7 ± 61.6	0.562
Estimated blood loss (ml)	189.6 ± 195.2	207.0 ± 218.8	0.658

Data were presented as the mean ± standard deviation or the n (percentage). The data were compared using Student t test for continuous data and the χ^2 test or Fisher's exact test for categorical data.
[a] Statistically significant difference.

Table 2
The VAS score of dysmenorrhea, hemoglobin, CA-125 in control and intervention groups.

	Control group $n = 61$	Intervention group $n = 54$	p
VAS score			
Baseline	6.9 ± 3.4	8.6 ± 1.6	0.006[a]
12 months after operation	2.2 ± 2.7	2.0 ± 2.3	0.667
24 months after operation	2.6 ± 3.0	2.4 ± 2.8	0.818
Hemoglobin (mg/dL)			
Baseline	11.7 ± 2.1	10.8 ± 2.3	0.037[a]
12 months after operation	12.7 ± 1.0	13.2 ± 1.6	0.144
24 months after operation	12.3 ± 1.8	13.0 ± 1.2	0.061
CA-125 (U/ml)			
before operation	114.1 ± 126.5	142.4 ± 145.7	0.276
12 months after operation	50.1 ± 44.0	24.5 ± 28.8	0.005[a]
24 months after operation	75.4 ± 68.5	28.6 ± 26.2	0.002[a]

Visual Analogue Scale (VAS).
The data were compared using Student t test for continuous data.
[a] Statistically significant difference.

Table 3
Mean difference of follow-up dysmenorrhea VAS score and hemoglobin.

	Control group $n = 61$	Intervention group $n = 54$	p
VAS score			
baseline-12th month	−4.1 ± 3.6	−6.5 ± 2.5	0.001[a]
baseline-24th month	−3.7 ± 3.7	−6.1 ± 2.7	0.002[a]
Hemoglobin (g/dL)			
baseline-12th month	1.0 ± 1.7 (n = 35)	2.1 ± 1.9 (n = 40)	0.008[a]
baseline-24th month	0.7 ± 1.8 (n = 27)	1.9 ± 2.1 (n = 31)	0.022[a]

The data were compared using Student t test for continuous data.
[a] Statistically significant difference.

Table 4
Pregnancy outcome.

	Control group $n = 61$	Intervention group $n = 54$
Pregnancy after the operation	7	2
Missed abortion	3	0
Live birth delivery	4	2

(from 78.6 ± 24.5 to 43.6 ± 13.7 U/ml). Our study showed similar results. Moreover, maintenance LNG-IUS prolonged the effect until a 24-month follow up.

The LNG-IUS expulsion rate is high in adenomyosis patients [14]. Even LNG-IUS placement after GnRH agonist therapy in adenomyosis patients still results in a 14.3% expulsion rate [23]. There were only two patients (2/31, 6.5%) who experienced expulsion of the device during 20 and 24 months after surgery in our study, which was possibly due to shrinkage of the uterine size after GnRH agonist administration, and normalization of the uterine cavity after the operation.

The pregnancy outcome was shown in Table 4. The intervention group had higher numbers of gravida and parity (Table 1), which indicated that for women who had completed childbearing but wished to preserve their uterus, LNG-IUS placement might be preferred. As previous studies mentioned, surgical adenomyomectomy may be associated with higher rate of future pregnancy complications [25]. The incidence of uterine rupture attributed to laparoscopic myomectomy was proposed to be 1% in Dubussion et al. [26]. In our study group, one 36-year-old female, gravida 3, para 2, alive 1, with a surgical history of hysterotomy, one cesarean section and laparoscopic adenomyomectomy, had uterine rupture over the uterine fundal wall during her third pregnancy at gestational age 30^{+4} weeks. Emergency cesarean section was performed, and the infant survived.

There were still some limitations in this study. First, high loss to follow up may occur in a retrospective study, and the information may not be completed. Second, patients with ovarian endometrioma and deep infiltrative endometriosis were not excluded in this study, which may affect the outcomes to a certain extent. Third, there were more than 50% leiomyomas in the final pathology reports. Although the leiomyoma may not affect the serum CA-125 level, it may have an influence on Hgb levels [27,28].

Since there were no statistical differences between three-month or six-month GnRH agonist therapy for dysmenorrhea or pelvic pain relief, in our study, the length of GnRH agonist therapy from three to six months were all included [29].

In conclusion, maintenance therapy with LNG-IUS is effective and well accepted for long-term therapy after conservative surgery for patients with adenomyosis. However, a larger RCT or a nationwide population-based cohort study is needed to assess the practical application.

Conflicts of interest

The authors declare no conflicts of interest relevant to this study.

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References

[1] Bragheto AM, Caserta N, Bahamondesa 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.

[2] Wood C. Surgical and medical treatment for adenomyosis. Hum Reprod Update 1998;4:323–36.

[3] Radzinsky VE, Khamoshina MB, Nosenko EN, Dukhin AO, A.Sojunov M, Orazmuradov AA, et al. Treatment strategies for pelvic pain associated with adenomyosis. Gynecol Endocrinol 2016;32:S19–22. https://doi.org/10.1080/09513590.2016.1232673.

[4] Sakhel K, Abuhamad A. Sonography of adenomyosis. J Ultrasound Med 2012;31:805–8.

[5] Fedele L, Bianchi S, Frontino G. Hormonal treatments for adenomyosis. Best Pract Res Clin Obstet Gynaecol 2008;22:333–9.

[6] Grimbizis G, Mikos T, Tarlatzis B. Uterus-sparing operative treatment for adenomyosis. Fertil Steril 2014;101:472–87.

[7] Younes G, Tulandi T. Conservative surgery for adenomyosis and results: a systematic review. J Minim Invasive Gynecol 2017. https://doi.org/10.1016/j.jmig.2017.07.014.

[8] Wang PH, Liu WM, Fuh JL, Cheng MH, Chao HT. Comparison of surgery alone and combined surgical-medical treatment in the management of symptomatic uterine adenomyoma. Fertil Steril 2009;28:876–85. https://doi.org/10.1016/j.fertnstert.2008.07.1744.

[9] Liu WM, Chen CH, Chiu LH, Tzeng CR. Long-term follow-up of severely symptomatic women with adenomyoma treated with combination therapy. Taiwan J Obstet Gynecol 2013;52:85–9.

[10] Jama FEA. Management of adenomyosis in subfertile women and pregnancy outcome. Oman Med J 2011;26:178–81.

[11] Struble J, Reid S, Bedaiwy MA. Adenomyosis: a clinical review of a challenging gynecologic condition. J Minim Invasive Gynecol 2016;23:164–85.

[12] Tsui KH, Lee WL, Chen CY, Sheu BC, Yen MS, Chang TC, et al. Medical treatment for adenomyosis and/or adenomyoma. Taiwan J Obstet Gynecol 2014;53:459–65.

[13] Lethaby A, Hussain M, Rishworth JR, Rees M. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding (Review). Cochrane Database Syst Rev 2015;(4).

[14] 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.

[15] Abou-Setta A, Houston B, Al-Inany H, Farquhar C. Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery. Cochrane Database Syst Rev 2013.

[16] Chen YJ, Hsu TF, Huang BS, Tsai HW, Chang YH, Wang PH. Postoperative maintenance levonorgestrel-releasing intrauterine system and endometrioma recurrence: a randomized controlled study. Am J Obstet Gynecol 2017;216:582e1–9.

[17] Chen YJ, Wang PH, Ocampo EJ, Twu NF, Yen MS, Chao KC. Single-port compared with conventional laparoscopic-assisted vaginal hysterectomy. Obstet Gynecol 2011;117:906–12.

[18] Horng HC, Chen CH, Chen CY, Tsui KH, Liu WM, Wang PH, et al. Uterine-sparing surgery for adenomyosis and/or adenomyoma. Taiwan J Obstet Gynecol 2014;53:3–7.

[19] Grimbizis GF, Mikos T, Zepiridis L, Theodoridis T, Miliaras D, C.Tarlatzis B, et al. Laparoscopic excision of uterine adenomyomas. Fertil Steril 2008;89:954–61.

[20] Hyams L. Adenomyosis; its conservative surgical treatment (hysteroplasty) in young women. N Y State J Med 1952;52:2778–84.

[21] Takeuchi H, Kitade M, Kikuchi I, Shimanuki H, Kumakiri J, Kitano T, et al. Laparoscopic adenomyomectomy and hysteroplasty: a novel method. J Minim Invasive Gynecol 2006;13:150–4.

[22] Pontis A, D'Alterio MN, Pirarba S, de Angelis C, Tinelli R, Angioni S. Adenomyosis: a systematic review of medical treatment. Gynecol Endocrinol 2016;32:696–700.

[23] Zhang P, Song K, Li L, Yukuwa K, Kong B. Efficacy of combined levonorgestrel-releasing intrauterine system with gonadotropin-releasing hormone analog for the treatment of adenomyosis. Med Princ Pract 2013;22:480–3.

[24] Zarchi MK, Zadeh ND, Sekhavat L, Nosouhi F. Correlation of CA-125 serum level and clinicopathological characteristic of patients with endometriosis. Int J Reprod Biomed 2016;14:713–8.

[25] Alvi FA, Glaser LM, Chaudhari A, Tsai S, Milad MP. New paradigms in the conservative surgical and interventional management of adenomyosis. Curr Opin Obstet Gynecol 2017;29:240–7.

[26] Dubuisson J-B, Fauconnier A, Deffarges J-V, Norgaard C, Kreiker G, Chapron C. Pregnancy outcome and deliveries following laparoscopic myomectomy. Hum Reprod 2000;15:869–73.

[27] Dawood MY, Khan-Dawood FS. Plasma insulin-like growth factor-I, CA-125, estrogen, and progesterone in women with leiomyomas. Fertil Steril 1994;61:617–21.

[28] Baker MF, Mccarthy J, Spellacy WN, Cardosi RP. Serum CA-125 levels in women with uterine leiomyomata and a review of the literature. J Gynecol Surg 2006;23:19–22.

[29] Hornstein MD, Heinrichs LR, Yuzpe AA, Veasy L, Buttram J, Burry KA, et al. Prospective randomized double-blind trial of 3 versus 6 months of nafarelin therapy for endometriosis associated pelvic pain. Fertil Steril 1995;63:955–62.