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Original Article

Postoperative maintenance levonorgestrel-releasing intrauterine system for symptomatic uterine adenomyoma

Ching-Jung Lin [a], Teh-Fu Hsu [a, b, c], Yen-Hou Chang [a, c], Ben-Shian Huang [a, c, d], Ling-Yu Jiang [a, c], Peng-Hui Wang [a, c, d], Yi-Jen Chen [a, c, d, e, *]

[a] Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan
[b] Department of Emergency Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[c] School of Medicine, National Yang-Ming University, Taipei, Taiwan
[d] Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan
[e] Department of Obstetrics and Gynecology, Cheng Hsin General Hospital, Taipei, Taiwan

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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

* Corresponding author. Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, School of Medicine, Institute of Clinical Medicine, National Yang-Ming University 201, Section 2, Shih-Pai Road, Taipei 11217, Taiwan. Fax: +886 (2) 7723 2788.
E-mail addresses: chenyj@vghtpe.gov.tw, chenyj58@gmail.com (Y.-J. Chen).

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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