Prevention of the recurrence of symptom and lesions after conservative surgery for endometriosis

Kaori Koga, M.D., Ph.D., Masashi Takamura, M.D., Ph.D., Tomoyuki Fujii, M.D., Ph.D., and Yutaka Osuga, M.D., Ph.D.

Department of Obstetrics and Gynecology, University of Tokyo, Tokyo, Japan

Although surgical excision of endometriosis both improves pain and enhances fertility, recurrence can further exacerbate pain and reduce fertility, which in turn impacts the quality of life and increases personal as well as social costs. Therefore, it is crucial to prevent the recurrence of symptoms and lesions after conservative surgery. This article reviews evidence regarding the prevention of postoperative recurrence of endometriosis reported since the 1990s. Over the past 5 years, many new studies have been conducted and have demonstrated that long-term postoperative medication markedly reduces the recurrence. Most of these studies used oral contraceptives (OC), with either the cyclic or continuous regimen, while some used oral or intrauterine progestin. Continuous OC is more efficacious than cyclic OC, especially for dysmenorrhea. The levonorgestrel-releasing intrauterine system is also shown to prevent recurrence of dysmenorrhea and possibly endometriosis lesions. Dienogest, a new progestin, is shown to reduce the recurrence of endometrioma. Similar to the case of ovarian endometriosis, long-term postoperative medication after conservative surgery for deep infiltrating or extragenital endometriosis seems important, although data are limited. Regardless of the lesion and the medication type, patients who discontinued medication experienced a higher incidence of recurrence, indicating that the protective effect of these medications seems to vanish rapidly after the discontinuation. On the basis of these facts, together with the pathogenesis of recurrence (retrograde menstruation and ovulation), regular and prolonged medication until the patient wishes to conceive is highly recommended to prevent the postoperative recurrence of endometriosis. (Fertil Steril® 2015;104:793–801. ©2015 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, recurrence, prevention, oral contraceptives, progestin

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Surgery is frequently selected for the treatment of endometriosis since medical treatment alone is often inadequate. Surgical excision of lesions (conservative surgery) has been shown to both improve pain and enhance fertility (1), and conservative surgery is preferred over radical surgery because most women with endometriosis are of reproductive age. Until the early 1990s, it was believed that the nature of endometriosis was "static" and that postoperative recurrence was relatively rare (2). However, a recent systematic review of the literature estimated the recurrence rate of endometriosis to be 21.5% at 2 years and 40%–50% at 5 years (3), which is much more frequent than previously believed. Although surgical excision of endometriosis both improves pain and enhances fertility, recurrence and repeated surgery can further exacerbate pain and reduce fertility (4), which in turn impacts quality of life and increases personal as well as social costs. Therefore, it is crucial to prevent the recurrence of symptoms and lesions after conservative surgery to maintain the improvement in pain and enhancement in fertility for as long as possible (5–8).

The purpose of this article is to review the evidence regarding the prevention of postoperative recurrence of endometriosis reported since the 1990s. We conducted a search of the MEDLINE database (http://www.nlm.nih.gov/medlineplus/) using

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Reprint requests: Kaori Koga, M.D., Ph.D., Obstetrics and Gynecology, University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113-8655, Japan (E-mail: kawotan-tky@umin.ac.jp).

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combinations of the following key words: "endometriosis," "endometrioma," "endometrial cyst," "recurrence," and "prevention." The search was limited to peer-reviewed, full-text articles in the English language published between January 1990 and July 2015. Randomized controlled trials (RCTs) with prospective and retrospective cohorts investigating the efficacy of postoperative medications prescribed for more than 6 months are described in the tables, although studies with shorter medication periods are discussed in the text. A manual search of review articles and cross-references completed the search.

Pathogenesis of Recurrences

There are two possible pathogeneses leading to the recurrence of endometrial lesions: regrowth of residual lesions and de novo lesion formation. Vignali et al. (9) found that the recurrence of deep endometriosis observed in a second operation often occurred in the same area of the pelvis that was involved in the first operation. With regard to endometrioma, the majority of recurrent cases (88.7%) involved the formerly treated ovary (3). It is also possible that regrowth can occur from a satellite lesion in areas with multiple endometriotic foci that are independent of the primary lesion (10). Surgery, especially conservative, is sometimes insufficient to completely remove these lesions; therefore, lesions frequently redevelop postoperatively.

Other studies suggested that recurrence may originate from de novo endometriosis lesions through retrograde menstruation (3). Bulletti et al. (11) reported that laparoscopy plus ablation of the endometrium effectively eliminated recurrence. This finding supports a role of eutopic endometrium in recurrence, although this evidence is challenged by the case of endometriosis recurrence after hysterectomy (12). In this context, it is interesting to introduce the notion that not only the retrograde endometrium but also ovulation may cause endometriosis, which is supported by the observation that ovarian endometrioma develops from a growing follicle (13) or the corpus luteum (14).

In comparison with endometriosis lesions, the pathogenesis of the recurrence of endometriosis-associated symptoms seems more complicated. A correlation has been demonstrated between the lesion site and pain (15); for instance, deep dyspareunia is associated with a deep lesion infiltrating the uterosacral and cardinal ligaments, the pouch of Douglas, the posterior vaginal fornix, or the anterior rectal wall (16). However, the recurrence of pain does not necessarily mean that a lesion recurred at that site.

Prevention of Symptom Recurrence

Regarding the recurrence of symptoms, studies conducted to evaluate the effect of postoperative medications on endometriosis-associated symptoms (i.e., dysmenorrhea, chronic pelvic pain, and dyspareunia) found that short-term therapy of 6 months of oral contraceptives (OCs) did not reduce the incidence of pain recurrence (9.1% vs. 17.1% for control at the 22-month follow-up) (17), suggesting that women experienced recurrence after OC cessation. An RCT comparing the efficacy between two OC regimens (cyclic and continuous administration) found no difference in the recurrence of pain (32% vs. 17%; $P=.23$) (18). However, the time frame (6 months) of this study was possibly too short to discern a difference, if any.

In contrast to short-term medical treatment, long-term (>6 months) administration of postoperative medications seems to prevent recurrence of symptoms (Table 1).

Dysmenorrhea, the most frequent symptom associated with endometriosis, can be successfully controlled by postoperative OCs (19–21) when used for >24 months, as demonstrated by the rate of lesion recurrence, which will be discussed later. Vercellini et al. (22) demonstrated that continuous use of monophasic OCs can control endometriosis-associated recurrent dysmenorrhea that does not respond to cyclic OC use (the mean visual analogue scale [VAS] score was 75 at baseline and 31 at the 2-year follow-up; $P<.01$). An RCT that compared the efficacy of 24-month cyclic OC, continuous OC, and surgery alone demonstrated that the frequency of recurrent dysmenorrhea was significantly lower in the cyclic (31%) or continuous (4%) OC group than in the surgery alone group (40%) and that the benefits of OC appeared earlier in the continuous group than in the cyclic group (6 vs. 18 months) (19). A similar trend for a preferable outcome in continuous OC users was also observed in a recent cohort study (9.4% vs. 20.9% for cyclic group; $P<.05$) (20). It is possible that the capacity of continuous OC to prevent or reduce the recurrence of dysmenorrhea could be due to inhibition of menses per se rather than to actual interference with pain mechanisms (23). It is also interesting to note that the benefit of continuous OC over cyclic OC regarding the prevention of lesion recurrence seems not as obvious as the prevention of symptom recurrence (24), suggesting that the effect of continuous OC in reducing symptom recurrence may not necessarily be a consequence of the effect on lesion recurrence.

In addition to OC, the levonorgestrel-releasing intrauterine system (LNG-IUS) reduces the recurrence of postoperative dysmenorrhea (25–27). A pilot cohort study confirmed that the use of LNG-IUS postoperatively prevented recurrence of moderate-to-severe dysmenorrhea compared with the surgery-only group (10% vs. 45%) (25). The effectiveness of postoperative LNG-IUS for relieving pain was also demonstrated in a double-blind RCT, which found that at 12 months, women in the LNG-IUS group achieved a greater reduction in dysmenorrhea than controls (reduction in dysmenorrhea VAS of −81.0 vs. −50.0 mm; $P<.001$) (27). On the other hand, two cohort studies compared the efficacy of LNG-IUS with that of other medications. Morelli et al. (21) revealed that in comparison with LNG-IUS use, OC use was markedly more effective in reducing the extent of pelvic pain (VAS of 29.0 vs. 19.1 mm; $P<.05$) and also disease recurrence (but not significantly), although patient satisfaction was markedly greater in the LNG-IUS group. Wong et al. (26) demonstrated that both LNG-IUS and depot medroxyprogesterone acetate (MPA) administered for 3 years after laparoscopy can inhibit dysmenorrhea and chronic pelvic pain recurrence, but LNG-IUS showed slightly higher pain reduction and better compliance.

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