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

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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
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 urogenital 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 −8.10 vs. −5.00 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.

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 −8.10 vs. −5.00 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.
### TABLE 1

List of studies that reported the efficacy of postoperative medications administered for more than 6 months on pain recurrence.

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>Year</th>
<th>Study design</th>
<th>Interventions</th>
<th>No. of patients</th>
<th>Follow-up period, mo</th>
<th>Outcome measured</th>
<th>Methods of measurement</th>
<th>Definition of recurrence</th>
<th>Results (recurrence rate)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vercellini et al.</td>
<td>22</td>
<td>2003</td>
<td>Cohort</td>
<td>Continuous OC</td>
<td>50</td>
<td>24</td>
<td>Dysmenorrhea</td>
<td>VAS, VRS</td>
<td>Not specified</td>
<td>mean VAS 75 → 31, mean VRS 2.4 → 0.7 LNG-IUS (10%)/EM (45%)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Vercellini et al.</td>
<td>25</td>
<td>2003</td>
<td>RCT</td>
<td>LNG-IUS/EM</td>
<td>20/20</td>
<td>12</td>
<td>(a) Dysmenorrhea</td>
<td>VAS</td>
<td>VAS &gt; 51</td>
<td>Median VAS reduction 17/10</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LNG-IUS/EM</td>
<td>5/7</td>
<td>12</td>
<td>(b) Chronic pelvic pain</td>
<td>VAS</td>
<td>Not specified</td>
<td>Median VAS reduction 31/15</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LNG-IUS/EM</td>
<td>9/8</td>
<td>12</td>
<td>(c) Dyspareunia</td>
<td>VAS</td>
<td>Not specified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seracchioli et al.</td>
<td>19</td>
<td>2010</td>
<td>RCT</td>
<td>Cyclic OC/continuous OC/EM</td>
<td>92/95/87</td>
<td>24</td>
<td>(a) Dysmenorrhea</td>
<td>VAS</td>
<td>VAS &gt; 40</td>
<td>Cyclic OC (31%)/continuous OC (4%)/EM (40%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cyclic OC/continuous OC/EM</td>
<td>92/95/87</td>
<td>24</td>
<td>(b) Chronic pelvic pain</td>
<td>VAS</td>
<td>VAS &gt; 40</td>
<td>Cyclic OC (29%)/continuous OC (27%)/EM (40%)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cyclic OC/continuous OC/EM</td>
<td>92/95/87</td>
<td>24</td>
<td>(c) Dyspareunia</td>
<td>VAS</td>
<td>VAS &gt; 40</td>
<td>Cyclic OC (35%)/continuous OC (29%)/EM (35%)</td>
<td>NS</td>
</tr>
<tr>
<td>Wong et al.</td>
<td>26</td>
<td>2010</td>
<td>RCT</td>
<td>LNG-IUS/MPA depot</td>
<td>15/15</td>
<td>36</td>
<td>(a) Pain score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>VRS</td>
<td>Not specified</td>
<td>Lower pain score with LNG-IUS only at 36M</td>
<td>&lt;.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LNG-IUS/MPA depot</td>
<td>15/15</td>
<td>36</td>
<td>(b) Dyspareunia</td>
<td>VRS</td>
<td>Not specified</td>
<td>No significant difference</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LNG-IUS/MPA depot</td>
<td>15/15</td>
<td>36</td>
<td>(c) Urinary/bowel symptoms</td>
<td>VRS</td>
<td>Not specified</td>
<td>No significant difference</td>
<td>NS</td>
</tr>
<tr>
<td>Tanmahasamut et al.</td>
<td>27</td>
<td>2012</td>
<td>RCT</td>
<td>LNG-IUS/EM</td>
<td>28/26</td>
<td>12</td>
<td>(a) Dysmenorrhea</td>
<td>VAS</td>
<td>Not specified</td>
<td>Lower VAS scores with LNG-IUS</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LNG-IUS/EM</td>
<td>28/26</td>
<td>12</td>
<td>(b) Chronic pelvic pain</td>
<td>VAS</td>
<td>Not specified</td>
<td>Lower VAS scores with LNG-IUS</td>
<td>&lt;.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LNG-IUS/EM</td>
<td>28/26</td>
<td>12</td>
<td>(c) Dyspareunia</td>
<td>VAS</td>
<td>Not specified</td>
<td>LNG-IUS did not influence score</td>
<td>NS</td>
</tr>
<tr>
<td>Morelli et al.</td>
<td>21</td>
<td>2013</td>
<td>Cohort</td>
<td>LNG-IUS/OC</td>
<td>44/48</td>
<td>24</td>
<td>Pain</td>
<td>VAS</td>
<td>Not specified</td>
<td>LNG-IUS (VAS 29.0)/OC (VAS 19.1)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Vlahos et al.</td>
<td>20</td>
<td>2013</td>
<td>Cohort</td>
<td>Cyclic OC/continuous OC</td>
<td>167/85</td>
<td>21/23</td>
<td>(a) Dysmenorrhea</td>
<td>Questionnaire&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not specified</td>
<td>Cyclic OC (20.9%)/continuous OC (9.4%)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cyclic OC/continuous OC</td>
<td>167/85</td>
<td>21/23</td>
<td>(b) Chronic pelvic pain</td>
<td>Questionnaire&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not specified</td>
<td>Cyclic OC (23.9%)/continuous OC (9.4%)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cyclic OC/continuous OC</td>
<td>167/85</td>
<td>21/23</td>
<td>(c) Dyspareunia</td>
<td>Questionnaire&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Not specified</td>
<td>Cyclic OC (17.3%)/continuous OC (10.5%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note: VRS — verbal rating score; EM — expectant management; NA — not available; NS — not significant.

<sup>a</sup> Dysmenorrhea plus chronic pelvic pain.
<sup>b</sup> Self-administered questionnaire (www.endometriosisfoundation.org/WERF-WHSSQuestionnaire-English.pdf).

In contrast to dysmenorrhea, control of postoperative recurrence of chronic pelvic pain (or nonmenstrual pain, noncyclic pain) and dyspareunia remains challenging. Regarding chronic pelvic pain, the above-mentioned RCT comparing the efficacy of postoperative cyclic OC, continuous OC, and surgery alone found no differences in chronic pelvic pain recurrence between patients treated with OC and those treated with surgery alone [19]. In contrast, the other above-mentioned recent cohort study found that the 2-year recurrence rate of nonmenstrual pelvic pain was lower in the continuous OC group than in the cyclic OC group (9.4% vs. 23.9%; P < .01) [20], although no comparison was available between OC users and nonusers in this study. The lower impact of OC administration on noncyclic pain in comparison with dysmenorrhea can be explained by the fact that dysmenorrhea is correlated with endometrial bleeding, which can be decreased or suppressed by OC use, while chronic pelvic pain is caused by different physiopathological mechanisms [23]. The effect of postoperative LNG-IUS on noncyclic pain also seemed to be limited in the above-mentioned pilot cohort study [25]. In contrast, the above-mentioned double-blind RCT found that LNG-IUS achieved a greater reduction in noncyclic pain than in the control group (VAS of −48.5 vs. −22.0 mm; P < .05) [27]; however, this reduction was less than that observed in dysmenorrhea. Collectively, as observed by the use of OCs, LNG-IUS also appears to be less beneficial in reducing the extent of noncyclic pain than the prevalence of dysmenorrhea, possibly because LNG-IUS does not suppress ovulation, which may be the main cause of noncyclic pain [28].

Regarding dyspareunia, there is no evidence of a positive effect of postoperative medical treatment, as neither cyclic or continuous OC regimens reduced the prevalence of symptoms [19, 20], as was also the case with LNG-IUS [27]. Furthermore, a 6-month study of placebo-controlled hormone therapy demonstrated that the placebo seemed to be more effective than hormone therapy for relief of dyspareunia [29]. The authors explained that this finding might be influenced by psychological factors that are dependent on personality, marital, and psychosexual issues [29].

Prevention of Ovarian Endometriosis (Endometrioma) Recurrence

Table 2 provides a list of studies that reported the efficacy of postoperative medications prescribed for more than 6 months on endometrioma recurrence.

OCs. The initial report of postoperative OC use for 6 months versus a control group demonstrated a significant difference in recurrence of both symptoms and endometrioma development between the two groups (6.2% vs. 10.2%; P = .041), whereas no significant differences were detected at 24 (9.4% vs. 13.6%) or 36 months (12.1% vs. 17.4%), suggesting that the use of OCs for 6 months can delay, but not prevent, long-term recurrence [17]. In contrast, all studies of postoperative OC use for 2 years or more demonstrated significant protective effects against recurrence of ovarian endometrioma [30]. A study of 277 patients showed that the 36-month cumulative proportion of subjects free from endometrioma recurrence was significantly greater than that of patients who used OC for the entire follow-up period (94% vs. 51%; P < .001) [30]. A cohort study of 73 patients demonstrated that the recurrence rate in those who used OC for 2 years was significantly lower than that for non-OC users or for patients who discontinued OC (2.9% vs. 35.8%; P < .001) [31]. Interestingly, recurrence is frequently observed in patients who discontinued OC. The same study reported recurrence in two of 14 (14.3%) women who discontinued OC use [31]. Likewise, a cohort study with a mean follow-up period of 38 months found a significant difference in ovarian endometrioma recurrence between always OC users (OC use during the entire follow-up period) and ever OC users (OC discontinued during the follow-up period; 0% vs. 55.5%; P < .05) [32]. In addition, women who used OC for shorter periods were at a higher risk for recurrence than those who used OC for longer periods. The 36-month cumulative proportion of subjects free from endometrioma recurrence was significantly greater among those who used OCs for 12 months or more than among those who used these agents for <12 months (78% vs. 51%; P < .001) [30]. Collectively, these findings demonstrate that postoperative OCs convey a protective effect against recurrence of ovarian endometrioma, but the effect seems to vanish rapidly after discontinuation.

Cyclic or Continuous? An RCT of 6-month administration of OCs found similar reductions in the recurrence of lesions in both cyclic and continuous regimens (1 of 28, 3.6% vs. 0 of 29; 0.0%) [18], although this time frame may have been too short to discern any difference, as also demonstrated by symptom recurrence. Another RCT of 24-month administration of OCs revealed that the crude recurrence rate within 24 months was significantly lower in the cyclic and continuous OC groups than in nonusers (14.7% and 8.2% vs. 29%); however, no significant differences were detected between the cyclic and continuous OC groups (P = .21) [24]. These investigators commented that although there was no statistically significant difference, there was a positive trend in size and growth of recurrent endometrioma among patients receiving continuous therapy [24]. A recent cohort study of 356 patients demonstrated a lower recurrence rate of endometrioma among women receiving continuous OC than among those receiving cyclic OC (16.6% vs. 9.2%; P < .005) [20]. These investigators suggested that continuous OC appears to offer significant advantages over cyclic OC [33].

Type of Progestin in OC: Does It Make a Difference? To determine whether the type of progestin used in OCs influences the protective efficacy of lesion recurrence, Cucinella et al. [34] recently compared the efficacy of three OC regimens with different progestins (i.e., desogestrel, gestodene, and dienogest) in an RCT but found no significant difference in the recurrence rate between these agents (26.5%, 31.8%, and 20.5%), although the recurrence rate in nonusers (74.7%) was significantly higher than that in all OC groups (P < .005).

Progestins. Dienogest is an estrane, a 19-nortestosterone derivative, with a very strong progesterogenic effect in the endometrium but with anti-androgenic activity [35]. A 24-week multicenter, randomized, open-label study demonstrated that dienogest was as effective as leuprolide acetate for
# TABLE 2

List of studies that reported the efficacy of postoperative medications administrated for more than 6 months on endometrioma recurrence.

<table>
<thead>
<tr>
<th>Author</th>
<th>Reference</th>
<th>Year</th>
<th>Study design</th>
<th>Interventions (when no duration is indicated, the duration is not limited)</th>
<th>No. of patients</th>
<th>Follow-up period, months</th>
<th>Outcome measured</th>
<th>Methods of measurement</th>
<th>Definition of recurrence</th>
<th>Results (recurrence rate)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Park et al.</td>
<td>40</td>
<td>2008</td>
<td>Cohort</td>
<td>GnRHa 6 months + OC (&lt;24/24–48/48&lt; months)</td>
<td>22/19/10</td>
<td>41 (19–94)</td>
<td>Endometrioma TV US</td>
<td>&gt;20 mm</td>
<td>OC &lt;24 (4.5%)/24–48 (0%)/48&lt; months (0%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Vercellini et al.</td>
<td>30</td>
<td>2008</td>
<td>Cohort</td>
<td>OC (always)/OC (ever)/EM</td>
<td>102/129/46</td>
<td>28 (median)</td>
<td>Endometrioma TV US</td>
<td>&gt;20 mm</td>
<td>OC (always) (6%)/EP (49%)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Takamura et al.</td>
<td>31</td>
<td>2009</td>
<td>Cohort</td>
<td>OC for 24 months/EM/GnRHa 3 or 6 months + OC/GnRHa 3 or 6 months alone</td>
<td>34/39/175/187</td>
<td>24/35 (12–114)</td>
<td>Endometrioma TV US</td>
<td>&gt;20 mm</td>
<td>OC (2.9%)/EM (43.5%)/GnRHa + OC (7.4%)/GnRHa alone (28.9%)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Seracchioli et al.</td>
<td>24</td>
<td>2010</td>
<td>RCT</td>
<td>Cyclic OC/continuous OC/EM</td>
<td>75/73/69</td>
<td>24</td>
<td>Endometrioma TV US</td>
<td>&gt;15 mm</td>
<td>Cyclic OC (14.7%)/continuous OC (8.2%)/EM (29%)</td>
<td>&lt;.005</td>
<td></td>
</tr>
<tr>
<td>Wong et al.</td>
<td>26</td>
<td>2010</td>
<td>RCT</td>
<td>LNG-IUS/MPA depot</td>
<td>15/15</td>
<td>36</td>
<td>Endometrioma TV US</td>
<td>&gt;30 mm</td>
<td>No recurrence were detected in both groups</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Morelli et al.</td>
<td>21</td>
<td>2013</td>
<td>Cohort</td>
<td>LNG-IUS/OC</td>
<td>44/48</td>
<td>24</td>
<td>Disease recurrence</td>
<td>CA125, TV US, pelvic exam</td>
<td>CA125 elevation and/or positive findings</td>
<td>LNG-IUS (20.5%)/OC (12.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Vlahos et al.</td>
<td>20</td>
<td>2013</td>
<td>Cohort</td>
<td>Cyclic OC/continuous OC at least 6 months</td>
<td>167/85</td>
<td>21/23</td>
<td>Endometrioma TV US</td>
<td>Not specified</td>
<td>Cyclic OC (16.6%)/continuous OC (9.2%)</td>
<td>&lt;.05</td>
<td></td>
</tr>
<tr>
<td>Cucinella et al.</td>
<td>34</td>
<td>2013</td>
<td>RCT</td>
<td>OC with desogestrel/OC with gestodene/OC with dienogest/EM</td>
<td>43/44/43/38</td>
<td>24</td>
<td>Endometrioma TV US</td>
<td>Not specified</td>
<td>Desogestrel (26.5%)/Gestodene (31.8%)/Dienogest (20.5%)/EM (74.7%)</td>
<td>&lt;.005 (all OC vs. EM)</td>
<td></td>
</tr>
<tr>
<td>Cho et al.</td>
<td>39</td>
<td>2014</td>
<td>Cohort</td>
<td>GnRHa 3 months followed by LNG-IUS/OC</td>
<td>42/57</td>
<td>17</td>
<td>Endometrioma TV US</td>
<td>&gt;20 mm</td>
<td>LNG-IUS (4.8%)/OC (10.5%)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Ouchi et al.</td>
<td>32</td>
<td>2014</td>
<td>Cohort</td>
<td>OC (always)/OC (ever)/Dienogest/GnRHa 6 months/EM</td>
<td>25/9/7/16/110</td>
<td>38.3</td>
<td>Endometrioma TV US</td>
<td>&gt;20 mm</td>
<td>OC (always) (0%)/OC (ever) (56%)/Dienogest (0%)/GnRHa (25%)/EM (23%)</td>
<td>&lt;.05 (OC always vs OC ever)</td>
<td></td>
</tr>
<tr>
<td>Ota et al.</td>
<td>38</td>
<td>2015</td>
<td>Cohort</td>
<td>Dienogest/EM</td>
<td>151/417</td>
<td>60</td>
<td>Endometrioma TV US</td>
<td>&gt;20 mm</td>
<td>Dienogest (4%)/EM (69%)</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

Note: TV US = transvaginal ultrasonography; EM = expectant management; NA = not available; NS = not significant.

relieving endometriosis-associated pain and was associated with a favorable safety profile and, therefore, can be considered an effective and well-tolerated treatment for endometriosis [36]. Dienogest was approved for the treatment of endometriosis in October 2007 in Japan and is also currently available in the European Union and Australia [37]. Ouchi et al. [33] reported no recurrence in seven patients who used postoperative dienogest over a mean follow-up period of 13.28 months. Very recently, Ota et al. [38] demonstrated that the cumulative recurrence rate at postoperative year 5 was significantly less in the 2-mg dienogest group than in the no postoperative medication group (69% vs. 4%; odds ratio = 0.09; 95% confidence interval = 0.03–0.26; P < 0.0001). The investigators suggested that although care should be taken to avoid development of metrorrhagia and decrease in bone mineral density, dienogest presents an alternative agent for a long-term postoperative management of endometriosis [38].

Wong et al. [26] demonstrated that both LNG-IUS and depot MPA administered for 3 years after laparoscopy can inhibit lesion recurrence (recurrence was not detected in any patient in either group). In this study, the authors also found that LNG-IUS was associated with better compliance (reduced vaginal bleeding) and greater safety (reduced bone mineral density loss) than MPA [26].

Two cohort studies compared the efficacy of OC to that of LNG-IUS. Morelli et al. [21] observed that OC use seemed more effective for the control of disease recurrence than LNG-IUS, but the difference was not significant (recurrence rate at 24 months, 12.5% vs. 20.5%; P = .30), although patient satisfaction was significantly greater in the LNG-IUS group (satisfaction rate at 24 months: 83.3% vs. 97.7%; P < .05). Cho et al. [39] reported that the recurrence rate during a median follow-up period of 17 months in women receiving LNG-IUS was comparable to that in women receiving OC after 3-month administration of a GnRH analogue (GnRHA: 4.8% vs. 10.5%) and concluded that postoperative use of a LNG-IUS seems to be as effective as the use of OC for the prevention of endometrioma recurrence.

Combinations of short-term GnRHAs and OCs. Two studies [40, 41] compared the use of GnRHa alone and GnRHa followed by long-term OC use and found that the incidence of endometrioma recurrence was significantly lower in the OC plus GnRHa group than in the GnRHa alone group. However, the impact of initial GnRHa administration was unclear. Given the inefficiency of short-term GnRHa use and the lack of a difference between administration of GnRHa for 3 or 6 months on the recurrence rate of subsequent OC use (P = .148) [41], it is questionable whether GnRHa administration before long-term OC use further reduced the risk of recurrence [5, 8].

Prevention of Deep Lesion Recurrence

Risk of postoperative recurrence and its prevention have also been reported in deep infiltrating endometriosis, although data are sparse [42]. According to a recent review, the recurrence rate after surgery observed in several studies varied between 5% and 25%, with most of the studies reporting 10% when considering a follow-up period of >2 years [43]. The recurrence rate appeared to be lower in the bowel resection anastomosis group than in the mixed study groups (full-thickness disc excision, bowel resection Anastomosis, and shave/superficial excision; total recurrence rate and the visually and/or histologically proven recurrence rates were 5.8% and 2.5% in the bowel resection Anastomosis group and 17.6% and 5.7% in the mixed study groups, respectively) [44]. A prospective study of 500 women managed for deep infiltrating rectovaginal endometriosis by shave excision demonstrated a low rate of recurrence (7.8%) within a follow-up period of 2–6 years [45]. In this prospective study, the rate of recurrence was very low among women who received continuous postoperative progestin (1%) and in those who had interrupted the medical treatment and rapidly conceived (2%), when compared with women who had abandoned treatment but did not become pregnant (20%); this suggests the importance of postoperative medical treatment among women who do not wish to conceive. A review article by Roman et al. [46] stated that continuous medical treatment can prevent recurrence of deep infiltrating endometriosis after surgical management and that instead of choosing either medical or surgical management, the two therapies should be combined to optimize effectiveness.

Prevention of Extragential Lesion Recurrence

Endometriosis also involves extragenital or extrapelvic organs, such as the diaphragm, abdominal wall, umbilicus [47], sciatic nerve [48], pleura, and lungs. Although surgical removal of symptomatic disease is recommended [49] and is commonly selected for management of extragenital endometriosis [50, 51], evidence of postoperative recurrence is extremely limited and discussed generally only in case reports. In addition, most case reports did not describe a long-term prognosis of more than 6 months and postoperative medication, if administrated, consisted of short-term (approximately 6 months) GnRHa administration [52, 53]. However, many cases experienced recurrence during the interval or after cessation of medical therapy [54–56], suggesting that long-term, constant, hormonal control is also important to prevent recurrence in extragenital endometriosis.

DISCUSSION

Summary of Evidence

Over the past 5 years, several studies have demonstrated that long-term postoperative medication markedly reduces the recurrence rates of endometriosis. Most of these studies used OC, with either the cyclic or continuous regimen, while some used oral or intrauterine progestin. Continuous OC is more efficacious than cyclic OC [20, 24], especially for dysmenorrhea (19), probably owing to inhibition of menses. Therefore, continuous OC is worth recommending to patients who have a higher risk of recurrence of dysmenorrhea. The LNG-IUS is also shown to prevent recurrence of dysmenorrhea [27] and possibly endometriosis lesion [26]. Given the fewer side effects and greater satisfaction [21],...
LNG-IUS presents an alternative option for patients who have a contraindication for, or poor compliance with, OC use. Di- enestriol, a new progestin, is shown to reduce the recurrence rate of endometrioma and is another alternative agent for long-term management (32, 38), although further comparisons should be made between the efficacy and long-term safety of the use of this agent and OCs. Regardless of the medication type, patients who discontinued medication experienced recurrence at a higher rate (30–32), indicating that the protective effect of these medications seems to vanish rapidly after discontinuation. Therefore, the medication should be continued until the patient wishes to conceive. Regarding the prevention of the recurrence of chronic pelvic pain and dyspareunia, evidence is very limited and further studies are needed. Postoperative long-term medical treatment is also encouraged after conservative surgery for deep infiltrating endometriosis (45, 46). In comparison with ovarian endometriosis, evidence is very limited regarding extragenital endometriosis; however, many cases experienced recurrence during the interval or after cessation of medical therapy (54–56), suggesting that long-term, constant, hormonal control is also important to prevent recurrence in these cases of endometriosis.

Mechanism by Which Long-term, but Not Short-term, Medication Prevents Recurrence

As described above, recurrence in endometriosis is a consequence of not only regrowth of residual lesions but also of the formation of de novo lesions (3), and as retrograde endometrium and ovulation (13, 14) cause de novo lesions, recurrence may occur as long as the patient continues to menstruate. Therefore, achieving a hypoestrogenic or hyperprogestogenic hormonal state using short-term GnRHa or progestin is ineffective because the menstrual cycles recover after the cessation of medication. Instead, medication that stops ovulation (i.e., OCs and systemic progestin), reduces menstrual bleeding (i.e., LNG-IUS and OCs), or stops menstruation (i.e., systemic progestin), which is associated with fewer adverse effects and higher compliance, can prevent recurrence if used over a long term.

Suggestions on Future Studies

Despite recent progress, additional comparisons should be made between the efficacy and long-term safety of the use of OCs and progestins and among the same drug types. Until what age should long-term management be recommended should also be determined. Moreover, although the use of postoperative medications was found to be effective to reduce the risk of recurrence, it is questionable whether such medications are beneficial to all patients. Therefore, further studies are necessary to develop novel markers to identify patients at high risk of recurrence who will truly benefit from such medications. A comprehensive survey is needed for cases with deep lesions and extragenital endometriosis to clarify whether the nature of endometriosis varies according to the organ involved. Efforts to improve current knowledge of endometriosis among nongynecological physicians, such as surgeons, dermatologists, and orthopedists, who may have opportunities to treat cases of extragenital endometriosis, should also be determined.
treatment of endometriosis recurrence inhibit ovulation; therefore, these agents cannot be prescribed to patients who currently wish to conceive. Hence, great efforts should be made to develop novel drugs that do not affect ovulation. Finally, although long-term use of OCs has been shown to provide protection against ovarian cancer among women with endometriosis (65), whether or not preventing recurrence after conservative surgery can prevent the development of endometriosis-associated cancer remains unknown, thus ultra-long-term follow-up studies are warranted.

Conclusion

In summary, regular and prolonged medications should be recommended after conservative surgery to prevent recurrence of endometriosis symptoms and lesions. Medications should be used until the patient wishes to conceive. As stated in the American Society for Reproductive Medicine committee opinion, endometriosis should be viewed as a chronic disease that requires lifelong management (66). Hence, short-sighted, temporary solutions should be avoided and lifelong management aimed to prevent recurrence should be emphasized.

REFERENCES


