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.

TABLE 1

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

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

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

[a] Dysmenorrhea plus chronic pelvic pain.

[b] Self-administered questionnaire (www.endometriosisfoundation.org/WERF-WHSSQuestionnaire-English.pdf).

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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 OC conveys 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 as 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 progestogenic 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.

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

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

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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; $P<.0001$). 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 GnRHa 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 Extragenital 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. Dienogest, 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.

A Paradigm Shift from "Short-term Treatment with Strong Drugs" to "Long-term Treatment with Drugs with Fewer Adverse Effects and Higher Compliance" is Recommended for Prevention of Recurrence

Most observational studies conducted up to the early 2000s have failed to find any evidence of the efficacy of postoperative medication for prevention of recurrence (57–60). Prospective studies using 3-month administration of GnRHa (61, 62), 6-month of danazol (63), and OC (17) have shown unsatisfactory results. Based on these studies, the online 2007 version of the European Society of Human Reproduction and Embryology (ESHRE) guidelines (http://guidelines.endometriosis.org/concise-pain.html) state that "post-operative hormonal treatment does not produce a significant reduction in pain recurrence at 12 or 24 months, and has no effect on disease recurrence."

In contrast, the studies conducted after the mid-2000s that are reviewed in this article evaluated long-term medical treatment of >6 months and selected OC or progestin, because these drugs are associated with fewer adverse effects and higher compliance and are therefore suitable for long-term use. On the basis of these results and those of a review article (8), the latest ESHRE guidelines were markedly revised in 2013, particularly the description of postoperative therapies (49), including recommendations such as, "After cystectomy for ovarian endometrioma in women not immediately seeking conception, clinicians are recommended to prescribe combined hormonal contraceptives for the secondary prevention of endometrioma" and "[i]n women operated on for endometriosis, clinicians are recommended to prescribe post-operative use of a LNG-IUS or a combined hormonal contraceptive for at least 18–24 months, as one of the options for these secondary prevention of endometriosis-associated dysmenorrhea, but not for non-menstrual pelvic pain or dyspareunia."

The term "secondary prevention" used in this description seems somewhat confusing because in preventative medicine, the term "secondary prevention" is defined as methods to detect and address an existing disease before the appearance of symptoms, while methods to reduce the negative impact of symptomatic disease are termed "tertiary prevention" (64). Therefore, the prevention of postoperative recurrence should have been termed "tertiary prevention" rather than "secondary prevention."

This recommendation should be acknowledged by all gynecologists outside of Europe as well as by nongynecological physicians, including surgeons, dermatologists, and orthopedists, who may also have opportunities to treat cases of extragenital 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 disease, should be made. Furthermore, now that minimally invasive surgery combined with medical treatment is preferred over radical surgery, it would be of interest to compare surgery plus medical treatment versus medical treatment alone. With regard to medications, all of the present options for the prevention or

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.

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Drospirenone induces decidualization in human eutopic endometrial stromal cells and reduces DNA synthesis of human endometriotic stromal cells

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Objective: To investigate the in vitro effect of drospirenone on human eutopic endometrial (EuSC) and ectopic endometriotic stromal cells (EcSC).
Design: Comparative and laboratory study. The experimental procedures were approved by the Institutional Review Board of the University of Tokyo (registration no. 0324-4).
Setting: University research laboratory.
Patients(s): Eight patients undergoing hysterectomy for benign gynecologic disease and 19 patients undergoing cystectomy or adnectomy for endometriosis.
Intervention(s): EuSC and EcSC were treated with drospirenone.
Main Outcome Measure(s): For the analysis of decidualization of EuSC, cells were observed using microscopy, and the production of PRL was measured using enzyme immunoassay. For the analysis of DNA synthesis of EcSC, 5-bromo-2'-deoxyuridine incorporation was measured by ELISA. Cells in apoptosis were detected and measured by flow cytometry.
Result(s): Drospirenone induced decidualization in EuSC, and the induction was negated by RU486. Drospirenone reduced DNA synthesis on EcSC, and this reduction was negated by RU486 or P receptor silencing, but not by aldosterone or mineralocorticoid receptor silencing. Drospirenone did not cause EcSC to undergo apoptosis.
Conclusion(s): Our study demonstrates the direct effects of drospirenone: decidualization of EuSC and reduced DNA synthesis of EcSC, but it does not cause EsSC apoptosis. (Fertil Steril® 2015;104:217–24. ©2015 by American Society for Reproductive Medicine.)
Key Words: Drospirenone, endometriosis, endometrium, decidualization, oral contraceptive(s)

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Drospirenone is a synthetic progestin that is similar to the natural hormone P and is a potent inhibitor of mineralocorticoid activity (1, 2). Similar to P, drospirenone displays high affinity for P receptors and mineralocorticoid receptors and low affinity for androgen receptors. Unlike P, which has considerable affinity for glucocorticoid receptor, drospirenone exhibits low binding to this receptor and is devoid of either glucocorticoid or antiglucocorticoid activity (1, 2). Clinically, drospirenone has been mainly used as a progestin in oral contraceptives (OCs) (3) and is expected to control endometriosis. As a constituent of OCs, 3 mg drospirenone significantly reduced the size of endometrioma and dysmenorrhea

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among patients with endometriosis (4). When used in the postoperative period, drospirenone-containing OC decreased anatomical symptoms and recurrence rates of endometrioma (5). Drospirenone also functions on the endometrium, reducing proliferation and thereby improving menorrhagia symptoms. Drospirenone has been shown to reduce Ki-67 expression in the human endometrium (6) and proliferation of mouse epithelial cells (7) when orally administered with and without E_2.

Despite the reported clinical impacts on the endometrium and endometriosis, the direct effects of drospirenone on the endometrium or endometriosis have not been well clarified.

To the best of our knowledge, the effect of drospirenone on the endometrium has been investigated in a single study. To investigate uterine bleeding in long-acting progestin users, Hampton et al. found that drospirenone, similar to other progestins, reduced MMP-1 and MMP-3 expression (8). The aim of this study was to clarify the direct effect of drospirenone on endometrial and endometriotic stromal cells, especially whether it induces decidualization in the endometrium and the anti-DNA synthesis effect on endometriosis.

MATERIALS AND METHODS

Reagents and Materials

Type I collagenase and deoxyribonuclease I were purchased from Wako. Antibiotics (a mixture of penicillin, streptomycin, and amphotericin B), 17β-estradiol, P, and aldosterone were obtained from Sigma. Dulbecco's modified Eagle's medium (DMEM)/F12 medium, 2.5% trypsin, HEPES, and 0.25% trypsin-EDTA were from Gibco. Charcoal/dextran-stripped fetal bovine serum (FBS) was from HyClone. RU486 (Mifepristone) was from Cayman Chemical. Drospirenone was provided by Bayer HealthCare.

Patients and Samples

The Institutional Review Board of the University of Tokyo approved this study, and written informed consent for use of the tissue was obtained from each woman. Endometrial tissues were obtained from endometrial tissue during hysterectomies on eight patients (aged 45 ± 1.07 years, mean ± SD). In each case, hysterectomies were for managing benign gynecological conditions such as uterine fibroid without endometrial pathologies. All patients had experienced regular menstrual cycles and had not received hormone therapy for at least 6 months before surgery. The specimens were dated according to each patient's menstrual history and standard histological criteria, according to Noyes et al. (9).

Endometriotic tissues were obtained from patients with ovarian endometriomas (n = 19, ages 36.9 ± 1.38 years, mean ± SD) who were undergoing laparoscopy or laparotomy. These patients had not received hormones or GnRH agonist for ≥3 months before surgery. Endometriotic tissue samples were obtained from the cyst wall of ovarian endometriomas under sterile conditions and transported on ice in DMEM/F12 to the laboratory.

Isolation and Culture of Human Eutopic Endometrial Stromal Cells (EuSC) and Ectopic Endometriotic Stromal Cells (EcSC)

Isolation and culture of human EuSC were as described elsewhere (10). Endometrial tissue was minced and incubated in DMEM/F12 containing 0.25% type I collagenase, 15 U/mL deoxyribonuclease I, 0.006% trypsin, and 0.02 mol/L HEPES for 60 minutes at 37°C. The resultant dispersed endometrial cells were separated by filtration through a 40-μm nylon cell strainer (BD Biosciences); dispersed EuSC passed through the strainer into the filtrate. EuSC in the filtrate were centrifuged and resuspended in DMEM/F12 containing 5% FBS and antibiotics. EuSC were plated in a 100-mm culture plate and maintained at 37°C in a humidified 5% CO_2/95% air atmosphere. At the first passage, the cells were plated at a density of 2×10^5 cells/well into 6-well culture plates.

EcSC were prepared as reported elsewhere (11–13). Endometriotic tissue was minced into small pieces, incubated in DMEM/F12 with 0.25% type I collagenase, 15 U/mL deoxyribonuclease I, 0.006% trypsin, and 0.02 mol/L HEPES for 1–2 hours at 37°C and filtered through 100-μm (aperture size) and then 70-μm nylon cell strainers. EcSC were cultured in DMEM/F12 containing 5% FBS and antibiotics. The purity of the stromal cells was >98%, as judged by positive cellular staining for vimentin and negative cellular staining for cytokeratin and CD45. More specifically, immunostaining with anti-CD10 antibody identified >95% of the cells as endometriotic stromal cells (13). At the first passage, the cells were plated at a density of 2×10^5 cells/well into 6-well culture plates or 96-well plates at 1×10^4 cells/well and incubated at 37°C in a humidified 5% CO_2/95% air environment.

In Vitro Decidualization of EuSC

To examine the effect of drospirenone on decidualization of EuSC, in vitro decidualization was achieved as described elsewhere (14). Briefly, after EuSC had reached 70% confluence in 6-well culture plates, they were rinsed and treated with 2.5% charcoal/dextran-stripped FBS in the presence of either E_2 (10^{-8} mol/L), P (10^{-7} mol/L), drospirenone (10^{-7} to 10^{-9} mol/L), E_2 (10^{-8} mol/L) plus P (10^{-7} mol/L), or E_2 (10^{-8} mol/L) plus drospirenone (10^{-7} to 10^{-9} mol/L). Previous studies have shown that P induces decidualization of EuSC in a dose-dependent manner (15), and in this study P was used as a positive control. The culture was terminated on the eighth day, when cells in the positive controls start to decidualize. We have confirmed that 8-day treatment of these hormones did not affect the cell number. To block binding to P receptors, EuSC were treated with P receptor antagonist RU486 (10^{-8} mol/L). Culture media were collected and replenished every 3 or 4 days. To evaluate decidualization, cells were observed using microscopy and the concentration of PRL in culture media collected on day 8 was determined.

Measurement of PRL

Concentrations of PRL in the media were measured using a specific enzyme immunoassay (EIA) kit (Cayman). The limit