

Recurrence of endometrioma after laparoscopic excision and its prevention by medical management

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1. ABSTRACT

Laparoscopic excision is considered as the ‘gold standard’ treatment of ovarian endometrioma. However, a frustrating aspect is that disease can recur. While laparoscopic excision is known to improve fertility, recurrence can cause significant ovarian damage and adverse affects on fertility. It is therefore crucial to prevent recurrence in order to conserve ‘improved’ fertility. Recurrence rates for endometrioma are reported from 11 to 32% within 1-5 years after excision. The recurrence rate is higher in patients with advanced endometriosis at surgery and in younger patients. Previous medical treatment for endometriosis prior laparoscopy is a risk factor for recurrence. Pregnancy soon after surgery has a protective effect for recurrence. The accumulating evidence suggests that the administration of oral contraceptives (OC), levonorgestrel-releasing intrauterine system (LNG-IUS) and a combination of gonadotropin releasing hormone (GnRH) analogue and OC may also have therapeutic benefits. Collectively, we propose that women should be well informed about the risks of endometrioma recurrence. We recommend that women who wish pregnancy should try conception as soon as possible. Further, we strongly advise hormonal therapy for patients, who do not want to conceive immediately, and until pregnancy is desired.

2. INTRODUCTION

Ovarian endometrioma is the most common form of endometriosis and accounts for 55% of this disorder (1). Regardless of its symptoms, surgery is the most frequently chosen treatment since medical treatment alone is inadequate (2). In addition, a possibility of malignant change in this disease is not negligible (3) (4). The European Society of Human Reproduction and Embryology (ESHRE) guidelines recommend that histology should be obtained to exclude malignancy in cases of endometrioma of more than 4 cm in diameter (5).

Because this disorder is commonly diagnosed in women of reproductive age (6), laparoscopic excision, instead of oophorectomy, is considered to be the ‘gold standard’ treatment of endometrioma (7). However, there is a frustrating aspect of treating endometrioma with laparoscopic excision, that is, a disease recurrence after surgery (8). While laparoscopic excision is known to improve fertility (9), recurrence and repeated surgery can cause significant ovarian damage and reduce fertility (10). Given that the majority of women who undergo this operation aim to conceive in the future, a dilemma arises: the physician plans laparoscopy, with the expectation that fertility should improve but he/she must also consider that

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Table 1. Postoperative recurrence rate of ovarian endometrioma by various studies

Author	Observation period	Recurrence rate	Ref.
Busacca <i>et al.</i> (1999)	48 months	11.7%	8
Ghezzi <i>et al.</i> (2001)	12 months	12.1%	25
Alborzi <i>et al.</i> (2004)	24 months	17.3%	15
Parazzini <i>et al.</i> (2005)	2 years	14.4%	16
Kikuchi <i>et al.</i> (2006)	60 months	31.7%	16
Koga <i>et al.</i> (2006)	24 months	30.4%	17
Vercellini <i>et al.</i> (2006)	36 months	12% *	29
Busacca (2006)	4 years	24.6%	33
Liu <i>et al.</i> (2007)	3 years	32.3%	14
Vercellini <i>et al.</i> (2008)	3 years	with OC 6%, without OC 49%	35

* recurrence was recorded by reoperation with histological confirmation, OC, oral contraceptives

recurrence can place fertility at risk. It is therefore crucial to prevent recurrence after laparoscopic excision in order to maintain 'improved' fertility for as long as possible (11).

When planning laparoscopy, gynecologists should be aware of each individual's expected likelihood of recurrence as well as her symptoms and desire for current or future pregnancy. By having information about factors related to the recurrence of ovarian endometrioma, gynecologists will be able to identify patients at risk, optimize the timing of laparoscopy and plan pre- and post-operative management properly. If there are strategies that prevent recurrence, gynecologists should provide patients with this information.

The aim of this review is to summarize factors that are proposed to influence the incidence of endometrioma recurrence, address the pathological mechanisms by which these factors affect recurrence, and review available evidence for the effect of post-operative medical management used to prevent recurrence. English language studies published in the last 20 years pertaining to the recurrence of endometrioma after laparoscopic excision and its related issues were identified through MEDLINE and PubMed. The basic criteria for article selection are indicated in each section.

3. RECURRENCE OF ENDOMETRIOMA AFTER LAPAROSCOPIC EXCISION

3.1. Recurrence rate

Up to the early 1990s, it was believed that the nature of endometriosis is 'static' and that the recurrence of endometrioma after laparoscopic excision is relatively rare (12). This may have been due to the limited availability of transvaginal ultrasound to detect endometrioma, and the large number of follow-up dropouts. In those days, patients were not informed of the risk of recurrence and did not see their physician unless they experienced pain or infertility. Further, physicians did not perform ultrasonography regularly, and therefore the real recurrence rate of endometrioma was undetermined (13). Since then, a number of studies have been conducted to determine the real recurrence rate of endometriosis, as a result recurrence is recognized as a much more frequent event than was previously believed. In this section, we will introduce various studies that investigated the post-operative recurrence rate of ovarian endometrioma.

Obviously, the recurrence rate varies with methods of surgery (excision of the cyst or ablation), the definition of recurrence (pain, detection of disease, requirement of reoperation) and the length of the follow-up period, therefore, these factors need to be considered when comparing studies. In regard to surgery methods, we included studies that only performed an excision of the cyst capsule as a mode of surgery. With regard to the definition of recurrence applied in this review, studies were selected on the basis of disease detection methods; studies that used ultrasonography to detect disease since this review focuses on the recurrence of endometrioma *per se* rather than on symptomatic recurrence.

Table 1 provides a list of published studies that report post-operative recurrence rates for ovarian endometrioma. Recurrence rates varied appreciably, ranging from 11 to 32% in 1 - 5 years. These variations could be related in part to definitions of recurrence; some authors defined recurrence by the presence of ovarian cysts greater than 3 cm in size (14, 15), while others defined by the presence of cysts of at least 2 cm (16, 17). Variation in patients' backgrounds such as age and rASRM stage may have also contributed to the range in recurrence rate. In this context, Guo reviewed 23 published studies that addressed endometriosis recurrence (including any site, and either subjective or objective findings of endometriosis) and statistically analyzed the correlation between recurrence rate versus the mean age of women at surgery, year of publication, type of endometriosis (ovarian endometrioma versus otherwise), type of study (comparative versus observational), percentage of rAFS stages III/IV patients included, and sample size (18). This analysis revealed that no variable except sample size was associated with recurrence rate. Smaller studies tended to report higher recurrence rates and the correlation was significant ($p = 0.0005$), however, the authors could not identify the cause (18). Further discussion will be continued in the following section on risk factors associated with recurrence.

The time between the surgery and recurrence is difficult to analyze. If patients are regularly followed-up, the time of recurrence can often be quantified accurately, however, not all may see their physician regularly because many are asymptomatic despite recurrence (8, 19). Therefore, it is not clear in which time period the patient is most vulnerable to recurrence, or whether there is a specific

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period of time after which a patient is less likely to develop recurrence. In 1991, Evers *et al.* reviewed the data from studies reporting recurrence and found that the recurrence rate during the first 5 years indicated a gradual increase. The authors consequently questioned whether endometriosis will eventually reappear in all patients who have had their visible lesions removed (13). Indeed, Liu *et al.* performed longitudinal analysis and found that the recurrence rates continued to increase with time, 7.8%, 17.7% and 32.3% at 1, 2, and 3 years respectively (14). On the contrary, Kikuchi *et al.* drew a cumulative recurrence rate curve and demonstrated that the cumulative rate reaches a plateau at around 48 months after surgery. Further studies with longer and careful follow-up are warranted to answer this issue.

It is still unknown whether the biological nature of recurrence is by *de novo* or the relapse of residual endometrioma. In order to distinguish these two types of recurrence, two studies analyzed endometrioma recurrence by 'per ovary' rather than by 'per patient' given that there can be two possibilities for the recurrence in case of recurrence on the operated ovary: *de novo* occurrence or persistence of residual endometriosis; on the contrary, in case of recurrence on the counter-lateral ovary, the disease is proposed to have developed by *de novo*. In this context, Exacoustos *et al.* analyzed 62 patients with recurrent endometrioma and found that 12 patients had recurrence on the counter-lateral untreated ovary (19). Kikuchi *et al.* also analyzed 26 cases with recurrence after hemi-lateral surgery and found that 11 cases had recurrence on the counter-lateral untreated ovary (16). The considerable risk of recurrence in the untreated ovary supports the *de novo* occurrence of endometrioma, although there is the possibility that a lesion undetected by the initial laparoscopy may have 'relapsed' after surgery. The time between the operation and the recurrence are also discussed in line with this issue. As discussed above, approximately 20% of recurrence occurs within 2 years after the surgery. On the other hand, endometriosis is thought to occur after 5 years (20) or as early as 3-4 years (21) of menarche. The comparison in time periods between surgery and recurrence (2 yrs), and menarche and onset of disease (3-5 years) suggests that recurrence occurs due to a relapse of residual endometriosis. Since the difference between *de novo* and relapse is critical for optimal management of this disorder, further studies with longer follow-ups and detailed observations are required to further illuminate this issue.

Collectively, there is no doubt that recurrence of endometrioma after laparoscopic excision is a common and serious problem, although the actual recurrence rate varies among studies. Further studies, to specifically identify the risk factors that contribute to recurrence are warranted and discussed in the following section.

3.2. Risk factors of recurrence

When planning laparoscopic excision of endometrioma, gynecologists should be aware of each individual's expected likelihood of recurrence. By having information about factors that may be related to the recurrence of ovarian endometrioma, gynecologists will be

able to distinguish patients at risk, optimize the timing of laparoscopy and plan pre- and post-operative management properly. In this section, we will introduce our own study (17) as well as others that aimed to identify risk factors of recurrence of endometrioma after laparoscopic excision.

Until the time we performed our study in 2005, recurrence of ovarian endometrioma after laparoscopy has always been discussed by focusing on a single factor such as the effect of post-operative (22) or pre-operative (23) medication, the method of laparoscopic procedure (24) and the anatomical location (25). Only one multivariate analysis analyzed six variables on the recurrence of endometrioma (8). Because multiple factors are assumed to influence recurrence, we designed an univariate analysis followed by a logistic regression analysis for 14 variables (age, presence of infertility, pain, uterine myoma, adenomyosis, previous medical treatment of endometriosis, previous surgery for ovarian endometriosis, single or multiple cysts, the size of the largest cyst at laparoscopy, unilateral or bilateral involvement, co-existence of deep endometriosis, rASRM score, post-operative medical treatment and post-operative pregnancy) to assess their independent effects on recurrence (17).

Table 2 displays the results of our univariate and logistic regression analysis of factors related to the recurrence of endometrioma. Using univariate analysis, age, presence of infertility, pain, uterine myoma, adenomyosis, previous surgery for ovarian endometrioma, single or multiple cysts, unilateral or bilateral involvement, co-existence of deep endometriosis, rASRM score and post-operative medical treatment did not significantly influence recurrence. Previous medical treatment of endometriosis and the larger diameter of the largest cyst appeared to be associated with higher recurrence, while post-operative pregnancy was associated with lower disease recurrence. According to a forward step-wise variable selection, five variables (previous medical treatment of endometriosis, the size of the largest cyst at laparoscopy, co-existence of deep endometriosis, rASRM score and post-operative pregnancy) were selected for logistic regression analysis. Significant factors that were independently associated with higher recurrence were previous medical treatment of endometriosis [rate of recurrence was 23.8% (29/112) versus 38.2% (39/102) in untreated versus treated patients, respectively, OR = 2.32, 95% CI = 1.23 - 4.38, P < 0.01] and larger diameter of the largest cyst (OR = 1.18, 95% CI = 1.00 - 1.39, P < 0.05). Neither co-existence of deep endometriosis nor higher rASRM score was significantly associated with recurrence. Post-operative pregnancy was significantly associated with lower recurrence [rate of recurrence 34.1% (63/185) versus 12.8% (5/39) in no pregnancy versus pregnancy group, respectively, OR = 10.29, 95% CI = 0.03 - 0.31, P < 0.05].

In addition to our study, we have summarized risk and favorable factors so far reported by others (Table 3). In general, the more advanced the endometriosis, the more the disease recurs. Larger cysts (17), and high rASRM scores (14, 16, 26-28) are reported to be risk factors for recurrence. Factors that may correlate with the

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Table 2. Univariate and logistic regression analysis of factors related to the recurrence of endometrioma

Factors	P values*	P values**	Odds ratios**	95%CI**
Age(y)	NS			
Infertility	NS			
Pain	NS			
Presence of uterine myoma	NS			
Presence of adenomyosis	NS			
Previous medical treatment of endometriosis	p < 0.05	p < 0.01	2.32	1.23 - 4.38
Previous surgery of ovarian endometrioma	NS			
Multiple cysts	NS			
Largest cyst diameter (cm)	p < 0.05	p < 0.05	1.18	1.00 - 1.39
Bilateral involvement	NS			
Co-existence of deep endometriosis	NS	NS	0.45	0.19 - 1.05
revised ASRM score	NS	NS	1.01	1.00 - 1.02
Post-operative medical treatment	NS			
Post-operative pregnancy	p < 0.05	p < 0.05	0.29	0.03 - 0.32

*univariate analysis, ** logistic regression analysis CI, confidence interval, ASRM, American Society for Reproductive Medicine. Reproduced with the permission of Ref (17)

Table 3. Risk / protective factors for the recurrence of endometrioma as reported by various studies

Authors (year)	Risk factors	Protective factors	Ref.
Busacca <i>et al.</i> (1999)	stage IV, previous surgery for endometriosis		8
Ghezzi <i>et al.</i> (2001)	left ovary involvement		25
Parazzini <i>et al.</i> (2005)	advanced stage, older age		26
Porpora <i>et al.</i> (2010)	previous surgery for endometriosis, high rASRM score, pelvic adhesions, ovarian stimulation drugs	post-operative pregnancy	28
Kikuchi <i>et al.</i> (2006)	high r-ASRM score, younger age		16
Koga <i>et al.</i> (2006)	larger cyst size, previous medical treatment	post-operative pregnancy	17
Vercellini <i>et al.</i> (2006)	short-term postoperative medical treatment		29
Busacca (2006)	age younger than 34	post-operative pregnancy	33
Liu <i>et al.</i> (2007)	high r-ASRM score, younger age, previous medical treatment		14
Vercellini <i>et al.</i> (2008)		OC use	35

r-ASRM, revised American Society for Reproductive Medicine; OC, oral contraceptives

severity of endometriosis such as previous medical treatment (14, 17), previous surgery for endometriosis (8, 28) and short-term post-operative medical treatment (29) are also identified as risk factors.

Reasons why previous medical treatment is a risk factor for recurrence can be explained as follows. Firstly, the medication may mask endometriotic lesions by causing atrophy, edema and reduction in size, so that they are undetected and escaped from removal at surgery. Secondly, hormonal suppressive therapies may alter the genomic characteristics of endometriotic lesions. As for the malignant transformation of endometriosis, it is proposed that hormonal ablative treatments may cause negative selection by suppressing the normal, eukaryotic cells more than aneuploid cells bearing chromosomal aberrations and increase the number of dyskaryotic cells in the endometriotic implants (30). This 'negative selection' may also contribute to the recurrence of endometriosis, making the lesion more active, progressive and prone to recurrence. Similarly, since endometriosis seems to be an epigenetic disease (31, 32), the previous use of medication may cause epigenetic changes that may increase the propensity for recurrence. Thirdly, it is also possible that if a patient has more aggressive-symptomatic disease, she is more likely to take medical treatment prior to surgery, which may confound the outcome.

Younger age at surgery is reported as a risk factor by two studies (14, 16). Younger age at surgery

would correlate with younger age at onset, and possibly a disease type that is more aggressive and prone to recurrence than the endometrioma associated with older age of onset. In addition, circulating estrogen levels after surgery may be higher in younger women and this may further contribute to recurrence in young patients.

The benefit of pregnancy on recurrence is observed in many reports (17, 28, 33). This is consistent with epidemiologic and clinical data showing that pregnancy has a protective effect on the development of endometriosis. An absence of retrograde menstruation and formation of corpus lutea (34), both of which are known to cause endometriosis, and persistent exposure to progesterone are thought to contribute to the protective effect of pregnancy. Post-operative OC use, which creates similar hormonal conditions to pregnancy, is also reported to provide protection against recurrence (35).

3.3. Post-operative medical managements to prevent recurrence

Despite the necessity, a gold-standard treatment modality of preventing recurrence after laparoscopic excision of endometrioma does not yet exist. Regarding pre-operative medical management, the 2004 Cochrane update concluded that hormonal therapy prior to surgery improves rAFS scores, but there is insufficient evidence of any effect on outcome (36), therefore in this review, we focus on post-operative medical management to prevent recurrence. As for post-operative medical management, the above-mentioned Cochrane review found that post-surgical

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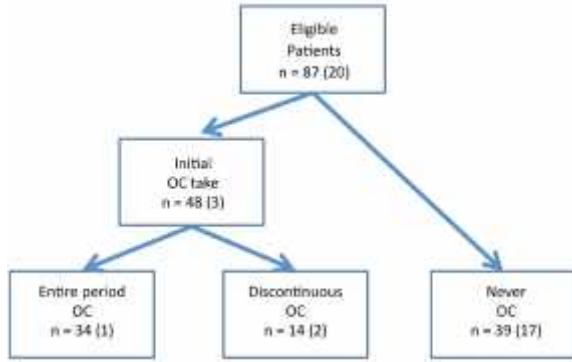


Figure 1. Flowchart of the patients who underwent laparoscopic excision of endometrioma in our retrospective cohort study. A total of 87 patients were followed up for 24 months. Of the 87 patients, 48 started to take OCs, but 39 did not. Of the 48 patients who had started OC, 34 continued OC for the entire study period (24 months), while 14 discontinued. Recurrence was detected in 20 out of 87 subjects (23.0%) in all study groups. To determine the effect of OC use on recurrence, we compared recurrence rates with patients who used OC for the entire study period (entire period OC group), patients who discontinued OC (discontinuous OC group) and patients who never used OC (never OC group). The recurrence rate was 2.9% (1/34), 14.3% (2/14) and 43.5% (17/39) in entire period OC, discontinuous OC and never OC group, respectively. Extracted with the permission of Ref (40)

hormonal suppression of endometriosis (either no medical therapy or placebo) significantly reduced disease recurrence (95% CI -4.02 - -0.58) than surgery alone (36). However, the Cochrane review added 'there is insufficient evidence to conclude that hormonal treatment in association with surgery is associated with a significant benefit' (36). Based on this review, an updated online version of the ESHRE guidelines (<http://guidelines.endometriosis.org/concise-pain.html>) mention that 'Compared to surgery alone or surgery plus placebo, 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'. As a result, it has remained controversial as to whether post-operative hormonal treatment can reduce disease recurrence.

The above quoted Cochrane meta-analysis (36) is based on studies that trialled post-operative medication for 3-6 months; for example 3 months gonadotropin releasing hormone (GnRH) analogue (37, 38), 6 months danazol (39) or oral contraceptives (OC) (22). However, the long-term effects of post-operative medication were not studied specifically. Since this meta-analysis, several studies evaluated long-term hormonal treatments with various hormonal drugs and their combination. In this review, articles were selected that evaluated the effect of post-operative hormonal treatments to prevent recurrence of endometrioma after laparoscopic excision, published from 2005, including our study (40).

As mentioned above, most studies included in the meta-analysis were short term (3-6 months). This time frame was probably used because of the risk of adverse effects associated with the hormonal treatments and cost of these therapies. In contrast to GnRH analogue or danazol, OC is inexpensive and has less adverse effects. In an attempt to investigate the effectiveness of long term OC, we conducted a before - after study. In 2005, our clinic introduced 'OC recommendation', that is, at the time of the operation, we provided each patient with information about OC; known possible benefits and risks and let the patient decide whether or not to take OC. Women who chose to take OC, were given a cyclic (21 days pills/ 7 days no pill), monophasic OC containing ethinyl-estradiol (0.035 mg) and norethisterone (1.0mg) (Ortho-M 21[®], Mochida, Tokyo, Japan), in the first menstrual cycle after the laparoscopy. We then conducted a historical study to compare the 2-year recurrence rate before and after the introduction of the 'OC recommendation'. The overall recurrence rate in patients who underwent laparoscopy after the introduction of the 'OC recommendation' was significantly lower than that in patients who received laparoscopy before the introduction (18.6 versus 33.1%, relative risk 0.56, 95% CI 0.32 - 0.97, $P < 0.05$) (40). The recurrence rate in those who used OC was significantly lower than others (non OC users plus those who quit OC), (2.9 versus 35.8%, relative risk 0.08, 95% CI 0.01 - 0.48, $P < 0.001$, Figure 1) (40). This study indicated that post-operative OC use reduces the risk of ovarian endometrioma after laparoscopic excision.

In addition to our study, there have been several studies that evaluate the role of post-operative OC on the recurrence of endometrioma. In contrast to the initial report showing OC had no effect on disease recurrence when used for up to 6 months (22), all studies that trialled post-operative OC for 2 years or more demonstrated protective effect of OC on recurrence (35, 40, 41). The different outcomes between short-term and long-term studies indicate that the duration of treatment with OC affects recurrence. Indeed, Vercellini *et al.* compared cumulative recurrence according to the duration of post-operative OC use and found that women who used OC for less than 12 months were at higher risk of recurrence than women using OC for 12 months or more (35).

The efficacy of post-operative progestin on the prevention of endometrioma recurrence has also been evaluated. Wong *et al* demonstrated that both levonorgestrel-releasing intrauterine system (LNG-IUS) and depot medroxyprogesterone acetate (MPA) administered for 3 years after laparoscopy can control disease recurrence (42). In this study, the authors also found that LNG-IUS showed a better compliance (reduced vaginal bleeding) and greater safety (reduced bone mineral density loss) (42). Although this study has a small sample size and did not provide conclusive results, it is interesting that long-term continuous progestin, which does not require daily intake, can potentially prevent recurrence.

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Regarding GnRH analogue therapy, two randomized studies were conducted to evaluate the short-term effect (post-operative 2 months or 6 months) and found no significant effect on the recurrence rate of ovarian endometriosis (43, 44). On the contrary, Jee *et al.* analyzed the influence of post-operative GnRH analogue according to the duration of the treatment, and found that 6-month treatment had a beneficial impact compared with 3-month and 4-month treatment and expectant management, although the differences did not reach statistical significance (45). It seems that GnRH analogue treatment longer than 6 months may reduce the recurrence, although this benefit should be weighed against the risk of adverse effects associated with the hormonal treatments.

Instead of increasing the duration of post-operative GnRH analogue treatment, a Korean group used OC followed by GnRH analogue as a 'maintenance therapy'. They trialed OC administration following 6 months of GnRH analogue therapy, and found that only 1/51 patients recurred in the median follow-up period of 41.2 months (46). Compared with the above-mentioned OC alone trials (35, 40, 41) this was an improved outcome. The same authors also compared patients who received 3-6 months of GnRH analogue therapy alone and patients who received OC after GnRH analogue and found that recurrent endometrioma after 60 months was significantly lower in OC plus GnRH analogue group than in GnRH analogue alone group (6.1 versus 43.3%) (47). Therefore, it seems that OC can 'maintain' the effect of initial GnRH analogue therapy, although further studies, comparing OC alone and OC in combination with GnRH analogue, are needed to evaluate the impact of initial GnRH analogue therapy.

Other trials involving aromatase inhibitor (letrozole) for 2 months (43) and dietary therapy (vitamins, minerals salts, lactic ferments, fish oil) for 6 months (44) have not affected recurrence. These therapies, however, were only administered for relatively short periods, and further trials are needed to assess their long-term effects. Combination therapy, such as hormonal therapy and dietary therapy may also be beneficial and should be trialed.

Although this review has focused on strategies to reduce recurrence, reducing post-operative ovarian damage is another important issue for women at a reproductive age. In this regard, if peri-operative management can control disease recurrence, we will be able to choose less invasive surgery such as ablative surgery and avoid compromising ovarian function. For example, a combination management using drainage, GnRH analogue administration and cauterization of the cyst wall has been trialed and led better outcome in terms of the preservation of the ovarian function (48, 49). Donnez *et al* also introduced a combined technique of excisional and ablative surgery along with three - month post-operative GnRH analogue and reported to achieve a higher pregnancy rate and a low recurrence rate (50). Medical management thus in turn expands the surgical options and further contributes to maintaining fertility.

4. SUMMARY AND PERSPECTIVE

The recurrence of endometrioma after laparoscopic excision is a very frequent event and women should be informed of this fact. This is especially true for patients who had advanced endometriosis at surgery, and young patients. Pregnancy after surgery has a protective effect for recurrence; therefore, women who wish pregnancy should be advised to try conception as soon as possible.

Regarding post-operative medical management for preventing recurrence, GnRH analogue and danazol have not been proved to be effective mainly because most trials used these drugs over short periods. In contrast, long-term administration of OC is safe and tolerable and recommended for those who do not want to conceive immediately after the surgery. Further studies are needed to determine the duration of OC treatment and to what age should OC treatment be recommended. LNG-IUS and combination therapies consisting of GnRH analogue and OC are also potential management strategies, although further long-term, controlled studies need to be conducted to prove their effectiveness.

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6. REFERENCES

1. S. Jenkins, D. L. Olive and A. F. Haney: Endometriosis: pathogenetic implications of the anatomic distribution. *Obstet Gynecol*, 67(3), 335-8 (1986)
2. K. D. Jones and C. J. Sutton: Laparoscopic management of ovarian endometriomas: a critical review of current practice. *Curr Opin Obstet Gynecol*, 12(4), 309-15 (2000)
3. M. Nishida, K. Watanabe, N. Sato and Y. Ichikawa: Malignant transformation of ovarian endometriosis. *Gynecol Obstet Invest*, 50 Suppl 1, 18-25 (2000)
4. H. Kobayashi, K. Sumimoto, N. Moniwa, M. Imai, K. Takakura, T. Kuromaki, E. Morioka, K. Arisawa and T. Terao: Risk of developing ovarian cancer among women with ovarian endometrioma: a cohort study in Shizuoka, Japan. *Int J Gynecol Cancer*, 17(1), 37-43 (2007)
5. S. Kennedy, A. Bergqvist, C. Chapron, T. D'Hooghe, G. Dunselman, R. Greb, L. Hummelshoj, A. Prentice and E. Saridogan: ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod*, 20(10), 2698-704 (2005)
6. L. C. Giudice and L. C. Kao: Endometriosis. *Lancet*, 364(9447), 1789-99 (2004)

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7. P. Beretta, M. Franchi, F. Ghezzi, M. Busacca, E. Zupi and P. Bolis: Randomized clinical trial of two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. *Fertil Steril*, 70(6), 1176-80 (1998)
8. M. Busacca, R. Marana, P. Caruana, M. Candiani, L. Muzii, C. Calia and S. Bianchi: Recurrence of ovarian endometrioma after laparoscopic excision. *Am J Obstet Gynecol*, 180(3 Pt 1), 519-23 (1999)
9. C. Chapron, P. Vercellini, H. Barakat, M. Vieira and J. B. Dubuisson: Management of ovarian endometriomas. *Hum Reprod Update*, 8(6), 591-7 (2002)
10. P. Vercellini, E. Somigliana, P. Vigano, S. De Matteis, G. Barbara and L. Fedele: The effect of second-line surgery on reproductive performance of women with recurrent endometriosis: a systematic review. *Acta Obstet Gynecol Scand*, 88(10), 1074-82 (2009)
11. P. Vercellini, E. Somigliana, P. Vigano, S. De Matteis, G. Barbara and L. Fedele: Post-operative endometriosis recurrence: a plea for prevention based on pathogenetic, epidemiological and clinical evidence. *Reprod Biomed Online*, 21(2), 259-65 (2010)
12. D. B. Redwine: Conservative laparoscopic excision of endometriosis by sharp dissection: life table analysis of reoperation and persistent or recurrent disease. *Fertil Steril*, 56(4), 628-34 (1991)
13. J. L. Evers, G. A. Dunselman, J. A. Land and P. X. Bouckaert: Is there a solution for recurrent endometriosis? *Br J Clin Pract Suppl*, 72, 45-50; discussion 51-3 (1991)
14. X. Liu, L. Yuan, F. Shen, Z. Zhu, H. Jiang and S. W. Guo: Patterns of and risk factors for recurrence in women with ovarian endometriomas. *Obstet Gynecol*, 109(6), 1411-20 (2007)
15. S. Alborzi, M. Momtahan, M. E. Parsanezhad, S. Dehbashi and J. Zolghadri: A prospective, randomized study comparing laparoscopic ovarian cystectomy versus fenestration and coagulation in patients with endometriomas. *Fertil Steril*, 82(6), 1633-7 (2004)
16. I. Kikuchi, H. Takeuchi, M. Kitade, H. Shimanuki, J. Kumakiri and K. Kinoshita: Recurrence rate of endometriomas following a laparoscopic cystectomy. *Acta Obstet Gynecol Scand*, 85(9), 1120-4 (2006)
17. K. Koga, Y. Takemura, Y. Osuga, O. Yoshino, Y. Hirota, T. Hirata, C. Morimoto, M. Harada, T. Yano and Y. Taketani: Recurrence of ovarian endometrioma after laparoscopic excision. *Hum Reprod*, 21(8), 2171-4 (2006)
18. S. W. Guo: Recurrence of endometriosis and its control. *Hum Reprod Update*, 15(4), 441-61 (2009)
19. C. Exacoustos, E. Zupi, A. Amadio, C. Amoroso, B. Szabolcs, M. E. Romanini and D. Arduini: Recurrence of endometriomas after laparoscopic removal: sonographic and clinical follow-up and indication for second surgery. *J Minim Invasive Gynecol*, 13(4), 281-8 (2006)
20. J. Fallon: Endometriosis in youth. *JAMA*, 131(17), 1405 (1946)
21. H. Hoshiai, M. Ishikawa, Y. Sawatari, K. Noda and T. Fukaya: Laparoscopic evaluation of the onset and progression of endometriosis. *Am J Obstet Gynecol*, 169(3), 714-9 (1993)
22. L. Muzii, R. Marana, P. Caruana, G. F. Catalano, F. Margutti and P. B. Panici: Postoperative administration of monophasic combined oral contraceptives after laparoscopic treatment of ovarian endometriomas: a prospective, randomized trial. *Am J Obstet Gynecol*, 183(3), 588-92 (2000)
23. L. Muzii, R. Marana, P. Caruana and S. Mancuso: The impact of preoperative gonadotropin-releasing hormone agonist treatment on laparoscopic excision of ovarian endometriotic cysts. *Fertil Steril*, 65(6), 1235-7 (1996)
24. A. Saleh and T. Tulandi: Reoperation after laparoscopic treatment of ovarian endometriomas by excision and by fenestration. *Fertil Steril*, 72(2), 322-4 (1999)
25. F. Ghezzi, P. Beretta, M. Franchi, M. Parissis and P. Bolis: Recurrence of ovarian endometriosis and anatomical location of the primary lesion. *Fertil Steril*, 75(1), 136-40 (2001)
26. F. Parazzini, C. Bertulesi, A. Pasini, M. Rosati, F. Di Stefano, S. Shonauer, M. Vicino, L. Aguzzoli, G. F. Trossarelli, M. Massobrio, G. Bracco, A. Perino, S. Moroni and P. Beretta: Determinants of short term recurrence rate of endometriosis. *Eur J Obstet Gynecol Reprod Biol*, 121(2), 216-9 (2005)
27. M. Busacca, S. Bianchi, B. Agnoli, M. Candiani, C. Calia, S. De Marinis and M. Vignali: Follow-up of laparoscopic treatment of stage III-IV endometriosis. *J Am Assoc Gynecol Laparosc*, 6(1), 55-8 (1999)
28. M. G. Porpora, D. Pallante, A. Ferro, B. Crisafi, F. Bellati and P. Benedetti Panici: Pain and ovarian endometrioma recurrence after laparoscopic treatment of endometriosis: a long-term prospective study. *Fertil Steril* (2008)
29. P. Vercellini, L. Fedele, G. Aimi, O. De Giorgi, D. Consonni and P. G. Crosignani: Reproductive performance, pain recurrence and disease relapse after conservative surgical treatment for endometriosis: the predictive value of the current classification system. *Hum Reprod*, 21(10), 2679-85 (2006)
30. Z. Blumenfeld: Hormonal suppressive therapy for endometriosis may not improve patient health. *Fertil Steril*, 81(3), 487-92 (2004)
31. S. W. Guo: Epigenetics of endometriosis. *Mol Hum Reprod*, 15(10), 587-607 (2009)
32. M. Izawa, F. Taniguchi, T. Uegaki, E. Takai, T. Iwabe, N. Terakawa and T. Harada: Demethylation of a

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nonpromoter cytosine-phosphate-guanine island in the aromatase gene may cause the aberrant up-regulation in endometriotic tissues. *Fertil Steril*, 95(1), 33-9 (2011)

33. M. Busacca, F. Chiaffarino, M. Candiani, M. Vignali, C. Bertulesi, G. Oggioni and F. Parazzini: Determinants of long-term clinically detected recurrence rates of deep, ovarian, and pelvic endometriosis. *Am J Obstet Gynecol*, 195(2), 426-32 (2006)

34. P. Vercellini, E. Somigliana, P. Vigano, A. Abbiati, G. Barbara and L. Fedele: 'Blood On The Tracks' from corpora lutea to endometriomas. *BJOG*, 116(3), 366-71 (2009)

35. P. Vercellini, E. Somigliana, R. Daguati, P. Vigano, F. Meroni and P. G. Crosignani: Postoperative oral contraceptive exposure and risk of endometrioma recurrence. *Am J Obstet Gynecol*, 198(5), 504 e1-5 (2008)

36. C. Yap, S. Furness and C. Farquhar: Pre and post operative medical therapy for endometriosis surgery. *Cochrane Database Syst Rev*(3), CD003678 (2004)

37. M. Busacca, E. Somigliana, S. Bianchi, S. De Marinis, C. Calia, M. Candiani and M. Vignali: Post-operative GnRH analogue treatment after conservative surgery for symptomatic endometriosis stage III-IV: a randomized controlled trial. *Hum Reprod*, 16(11), 2399-402 (2001)

38. G. Loverro, C. Carriero, A. C. Rossi, G. Putignano, V. Nicolardi and L. Selvaggi: A randomized study comparing triptorelin or expectant management following conservative laparoscopic surgery for symptomatic stage III-IV endometriosis. *Eur J Obstet Gynecol Reprod Biol*, 136(2), 194-8 (2008)

39. S. Bianchi, M. Busacca, B. Agnoli, M. Candiani, C. Calia and M. Vignali: Effects of 3 month therapy with danazol after laparoscopic surgery for stage III/IV endometriosis: a randomized study. *Hum Reprod*, 14(5), 1335-7 (1999)

40. M. Takamura, K. Koga, Y. Osuga, Y. Takemura, K. Hamasaki, Y. Hirota, O. Yoshino and Y. Taketani: Post-operative oral contraceptive use reduces the risk of ovarian endometrioma recurrence after laparoscopic excision. *Hum Reprod*, 24(12), 3042-8 (2009)

41. R. Seracchioli, M. Mabrouk, C. Frasca, L. Manuzzi, G. Montanari, A. Keramyda and S. Venturoli: Long-term cyclic and continuous oral contraceptive therapy and endometrioma recurrence: a randomized controlled trial. *Fertil Steril*, 93(1), 52-6 (2010)

42. A. Y. Wong, L. C. Tang and R. K. Chin: Levonorgestrel-releasing intrauterine system (Mirena) and Depot medroxyprogesterone acetate (Depoprovera) as long-term maintenance therapy for patients with moderate and severe endometriosis: a randomised controlled trial. *Aust N Z J Obstet Gynaecol*, 50(3), 273-9 (2010)

43. S. Alborzi, B. Hamed, A. Omidvar, S. Dehbashi and M. Alborzi: A comparison of the effect of short-term aromatase inhibitor (letrozole) and GnRH agonist (triptorelin) versus case control on pregnancy rate and symptom and sign recurrence after laparoscopic treatment of endometriosis. *Arch Gynecol Obstet* (2010)

44. F. Sesti, T. Capozzolo, A. Pietropolli, M. Marziali, M. R. Bollea and E. Piccione: Recurrence rate of endometrioma after laparoscopic cystectomy: a comparative randomized trial between post-operative hormonal suppression treatment or dietary therapy vs. placebo. *Eur J Obstet Gynecol Reprod Biol*, 147(1), 72-7 (2009)

45. B. C. Jee, J. Y. Lee, C. S. Suh, S. H. Kim, Y. M. Choi and S. Y. Moon: Impact of GnRH agonist treatment on recurrence of ovarian endometriomas after conservative laparoscopic surgery. *Fertil Steril*, 91(1), 40-5 (2009)

46. H. J. Park, Y. A. Koo, B. K. Yoon and D. Choi: Postoperative long-term maintenance therapy with oral contraceptives after gonadotropin-releasing hormone analog treatment in women with ovarian endometrioma. *J Minim Invasive Gynecol*, 16(1), 34-9 (2009)

47. D. Y. Lee, D. S. Bae, B. K. Yoon and D. Choi: Post-operative cyclic oral contraceptive use after gonadotrophin-releasing hormone agonist treatment effectively prevents endometrioma recurrence. *Hum Reprod*, 25(12), 3050-4 (2010)

48. D. Tsolakidis, G. Pados, D. Vavilis, D. Athanatos, T. Tsalikis, A. Giannakou and B. C. Tarlatzis: The impact on ovarian reserve after laparoscopic ovarian cystectomy versus three-stage management in patients with endometriomas: a prospective randomized study. *Fertil Steril*, 94(1), 71-7 (2010)

49. G. Pados, D. Tsolakidis, E. Assimakopoulos, D. Athanatos and B. Tarlatzis: Sonographic changes after laparoscopic cystectomy compared with three-stage management in patients with ovarian endometriomas: a prospective randomized study. *Hum Reprod*, 25(3), 672-7 (2010)

50. J. Donnez, J. C. Lousse, P. Jadoul, O. Donnez and J. Squifflet: Laparoscopic management of endometriomas using a combined technique of excisional (cystectomy) and ablative surgery. *Fertil Steril*, 94(1), 28-32 (2010)

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