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Recurrence of ovarian endometrioma after laparoscopic excision

K.Koga, Y.Takemura, Y.Osuga[1], O.Yoshino, Y.Hirota, T.Hirata, C.Morimoto, M.Harada, T.Yano and Y.Taketani

Department of Obstetrics and Gynecology, University of Tokyo, Japan

[1]To whom correspondence should be addressed at: Department of Obstetrics and Gynecology, University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113-8655, Japan. E-mail: yutakaos-tky@umin.ac.jp

BACKGROUND: To analyse risk factors that influence the recurrence of endometrioma after laparoscopic excision. METHODS: A total of 224 patients who had a minimum of 2 years of post-operative follow-up after laparoscopic ovarian endometrioma excision were studied retrospectively. Recurrence was defined as the presence of endometrioma more than 2 cm in size, detected by ultrasonography within 2 years of surgery. Fourteen 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, revised American Society for Reproductive Medicine (ASRM) score, post-operative medical treatment and post-operative pregnancy) were evaluated to assess their independent effects on the recurrence using logistic regression analysis. RESULTS: The overall rate of recurrence was 30.4% (68/224). Significant factors that were independently associated with higher recurrence were previous medical treatment of endometriosis [odds ratio (OR) = 2.324, 95% confidence interval (95% CI) = 1.232–4.383, *P* = 0.0092) and larger diameter of the largest cyst (OR = 1.182, 95% CI = 1.004–1.391, *P* = 0.0442). Post-operative pregnancy was associated with lower recurrence (OR = 0.292, 95% CI = 0.028–0.317, *P* = 0.0181). CONCLUSIONS: Previous medical treatment of endometriosis or large cyst size was a significant factor that was associated with higher recurrence of the disease. Post-operative pregnancy is a favourable prognostic factor.

Key words: endometriosis/laparoscopy/ovary/recurrence/risk factors

Introduction

Ovarian endometrioma is a common disease lesion among women with endometriosis. Regardless of its symptoms, surgery is most frequently chosen for its treatment because medical treatment alone is inadequate (Jones and Sutton, 2000). In addition, a likelihood of malignant change in this disease is not negligible (Nishida *et al*., 2000), and 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 3 cm in diameter (Kennedy *et al*., 2005).

Because this disorder is commonly diagnosed in women of reproductive age (Giudice and Kao, 2004), laparoscopic excision of endometrioma, instead of oophorectomy, is applied for most cases. When it is done in infertile woman, laparoscopic excision is also known to improve fertility (Beretta *et al*., 1998).

One of the most frustrating aspects of treating endometrioma with laparoscopic excision is disease recurrence after surgery (Busacca *et al*., 1999). When planning a laparoscopy, gynaecologists should be aware of each individual's expected likelihood of recurrence as well as her symptoms and desire for current or future fertility. By having information about factors that may be related to a recurrence of ovarian endometrioma, gynaecologists will be able to distinguish patients at risk, optimize the timing of laparoscopy and plan pre- and post-operative management properly. However, little study has been done to analyse various variants that may have impacts on a recurrence of endometrioma after laparoscopic excision.

To date, recurrence of ovarian endometrioma after laparoscopy has always been discussed focusing on a single factor, such as the effect of post-operative (Muzii *et al*., 2000) or pre-operative (Muzii *et al*., 1996) medication, the method of laparoscopic treatment (Saleh and Tulandi, 1999) and the anatomical location (Ghezzi *et al*., 2001). There is only one multivariate analysis that analysed six variables on the recurrence of

endometrioma by Busacca *et al*. (1999). To analyse risk factors that might influence the recurrence of endometrioma after laparoscopic excision, we retrospectively evaluated 14 variables to assess their independent effects on the recurrence.

Materials and methods

Subjects

A total of 224 patients who had a minimum of 2 years of post-operative follow-up after laparoscopic ovarian endometrioma excision performed at University of Tokyo Hospital between 1995 and 2002 were studied retrospectively. Patient characteristics are summarized in Table I. Institutional Review Board approval was not requested because laparoscopic excision of endometrioma is the standard treatment used in our department. All the procedures followed were in accordance with the revised Declaration of Helsinki, and patients gave informed consent before surgery.

We did not routinely administer pre- or post-operative medical therapy, however, some of the patients were given medical therapy according to their specific needs, e.g. relief of pain. One hundred and two patients had undergone medical treatment previously. Among them, 65 had continued their medication until the operation. The average duration of pre-operative medical therapy was 9.7 months. Post-operative medical therapy was given in 32 cases. The average duration of post-operative medical therapy was 9.5 months. More detailed information about the medication is summarized in Table II.

Surgery

Laparoscopic excision of ovarian endometrioma was performed as follows. After inspection of the pelvis, the ovary was freed from any adhesions. A sharp cortical incision was made, and a cleavage plane was identified. The capsule of the cyst was stripped away from the normal ovarian tissue completely, using bilateral traction and sharp dissection. Other endometriotic peritoneal implants were excised with scissors or coagulated with bipolar electrocoagulation completely, whereas a part of deep endometriosis might be left untreated. Haemostasis was accurately achieved with bipolar electrocoagulation.

The recurrence of ovarian endometrioma was defined as the presence of cysts with a typical aspect detected by transvaginal ultrasonography (Exacoustos *et al*., 2003) more than 2 cm in diameter within 2 years of surgery. When the cyst was indistinguishable from a transient corpus luteum cyst or an intraovarian haematoma, the diagnosis of recurrence was made only when the cyst had not disappeared after several successive menstrual cycles. Fourteen 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 (see abstract) at laparoscopy, unilateral or bilateral involvement, co-existence of deep endometriosis, revised american society for reproductive medicine (ASRM) score, post-operative medical treatment and post-operative pregnancy] were evaluated to assess their effects on the recurrence of ovarian endometrioma. The pain was defined as requiring analgesia at least once a month for dysmenorrhea or chronic pelvic pain. Univariate analysis of the possible risk factors for recurrence followed by a forward step-wise variable selection and logistic regression analysis were performed to eliminate confounding factors. A P value of less than 0.05 was considered statistically significant.

Table I. Characteristics of patients

Factors	Number of cases (%)
Age (years)	32.2 ± 5.4[a]
Infertility	76 (33.9)
Pain	131 (58.5)
Presence of uterine myoma	18 (8.1)
Presence of adenomyosis	60 (26.9)
Previous medical treatment of endometriosis	102 (45.5)
Previous surgery of ovarian endometrioma	30 (13.4)
Multiple cysts	98 (43.8)
Largest cyst diameter (cm)	5.2 ± 1.9[a]
Bilateral involvement	85 (37.9)
Co-existence of deep endometriosis	63 (28.1)
Revised ASRM score	58.1 ± 32.2[a]
Post-operative medical treatment	32 (14.2)
Post-operative pregnancy	39 (17.4)

ASRM, American Society for Reproductive Medicine
[a]Mean ± SD.

Table II. Number of patients who underwent medical treatment before and after the operation

Treatment	Number of patients who underwent medical treatment	
	Before operation	After operation
GnRH agonist	87	15
Danazol	21	5
Oral contraceptives	5	15

Results

The overall rate of recurrence was 30.4% (68/224). Table III presents P values, odds ratio (OR) and 95% confidence interval (95% CI) of univariate and logistic regression analysis.

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 and post-operative medical treatment did not significantly influence recurrence. Previous medical treatment of endometriosis, larger diameter of the largest cyst and higher revised ASRM score appeared to be associated with higher recurrence, whereas 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, revised ASRM 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 25.5% (29/112) versus 38.2% (39/102) in untreated versus treated patients, respectively, OR = 2.324, 95% CI = 1.232–4.383, P = 0.0092] and larger diameter of the largest cyst (OR = 1.182, 95% CI = 1.004–1.391, P = 0.0442). Neither co-existence of deep endometriosis nor higher revised ASRM score was significantly associated with recurrence. Post-operative pregnancy was significantly associated with lower recurrence [rate of recurrence was 34.1% (63/185) versus 12.8% (5/39) in no pregnancy versus pregnancy group, respectively, OR = 0.292, 95% CI = 0.028–0.317, P = 0.0181].

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

Factors	Univariate analysis	Logistic regression analysis	
	P values	*P* values	Odds ratio (95% confidence interval)
Age (years)	NS		
Infertility	NS		
Pain	NS		
Presence of uterine myoma	NS		
Presence of adenomyosis	NS		
Previous medical treatment of endometriosis	<0.05	<0.01	2.324 (1.232–4.383)
Previous surgery of ovarian endometrioma	NS		
Multiple cysts	NS		
Largest cyst diameter (cm)	<0.05	<0.05	1.182 (1.004–1.391)
Bilateral involvement	NS		
Co-existence of deep endometriosis	NS	NS	0.456 (0.198–1.052)
Revised score	NS	NS	1.010 (1.000–1.021)
Post-operative medical treatment	NS		
Post-operative pregnancy	<0.05	<0.05	0.292 (0.028–0.317)

ASRM, American Society for Reproductive Medicine

Discussion

Many previous studies discussed the recurrence of ovarian endometrioma after laparoscopic excision, in view of requirements of reoperation (Busacca *et al*., 1999; Saleh and Tulandi, 1999; Abbott *et al*., 2003) or pain recurrence (Busacca *et al*., 1999; Abbott *et al*., 2003). In this study, we focused on the mechanism of ovarian endometrioma recurrence *per se* and used a definition of the recurrence as the presence of cysts more than 2 cm in diameter by ultrasonography, which might be rather objective and cover minimum lesions. Under this definition, we observed a recurrence rate of 30.4%.

The patient's age, presence of infertility and pain did not significantly influence the recurrence. The presence of neither uterine myoma nor adenomyosis was significant. As for the characteristics of endometrioma, single or multiple cysts and unilateral or bilateral ovarian involvement were not significant, whereas patients with larger endometrioma had higher probability of recurrence, which agrees with the finding of earlier studies (Busacca *et al*., 1999; Saleh and Tulandi, 1999). Because most ovarian endometrioma are associated with extra ovarian endometriosis (Redwine, 1999), we evaluated revised ASRM score and co-existence of deep endometriosis. Revised ASRM score did not independently correlate the recurrence. Co-existence of deep endometriosis did not influence the recurrence either.

A new observation demonstrated in this study was that previous medical treatment of endometriosis was a significant factor that was associated with higher recurrence, whereas previous surgery of ovarian endometrioma was not. The less-favourable prognosis for women who have already had medical treatment may be explained by two possible reasons. The first is that the medication may mask endometriotic lesions and allow them to escape from removal at operations. Because more than half of the women who were categorized into previous medical treatment group had continued their medication until the time of operation, it may be possible that the medication might yield latent lesions that remain and recur after the operation. Our findings may also support the study of Muzii *et al*. (1996), which suggests that pre-operative GnRH agonist treatment does not seem to offer any advantage in terms of surgical performance based on various parameters including recurrence rates.

The second possible reason for negative impact of medical treatment on endometrioma recurrence is that hormonal suppressive therapy may alter some genomic characteristics of endometriotic lesions. As for malignant transformation of endometriosis, it is proposed that hormonal ablative treatments may cause negative selection, suppress the normal, eukaryotic cells more than aneuploid cells bearing chromosomal aberrations and increase the rate of dyskaryotic cells in the endometriotic implants (Blumenfeld, 2004). We suppose that the 'negative selection' may also contribute to the recurrence of disease, making the lesion more active, progressive and prone to recurrence.

Patient with post-operative pregnancy had a much lower rate of recurrence, which indicates that subsequent pregnancy may have a protective effect on endometrioma recurrence. On the contrary, laparoscopic excision of endometrioma is known to improve fertility, when it is done in infertile women (Beretta *et al*., 1998). Taken together, gynaecologists should optimize the timing of laparoscopy according to the patient's desire for current and future pregnancy.

Our study was in line with previous observations that post-operative medical treatment did not significantly influence disease recurrence (Bianchi *et al*., 1999; Muzii *et al*., 2000; Busacca *et al*., 2001). Three-month GnRH analogue (Busacca *et al*., 2001) or danazol (Bianchi *et al*., 1999) therapy after laparoscopy was demonstrated to provide no significant advantage in preventing disease recurrence. Post-operative administration of low-dose cyclic oral contraceptives for 6 months had also no significant effect on the long-term recurrence rate of endometrioma (Muzii *et al*., 2000). However, the treatment period of these studies, and also ours, was less than 1 year, and there is no information about the effect of longer period of treatment. It is therefore possible that medical treatments longer than 1 year may have an effect to prevent endometrioma recurrence. Further studies, e.g. randomized controlled trials, are needed to determine the effectiveness of these therapies.

In summary, this study demonstrated significant factors that were independently associated with a higher or lower recurrence of endometrioma after laparoscopic excision.

References

Abbott JA, Hawe J, Clayton RD and Garry R (2003) The effects and effectiveness of laparoscopic excision of endometriosis: a prospective study with 2-5 year follow-up. Hum Reprod 18,1922–1927.

Beretta P, Franchi M, Ghezzi F, Busacca M, Zupi E and Bolis P (1998) Randomized clinical trial of two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. Fertil Steril 70,1176–1180.

Bianchi S, Busacca M, Agnoli B, Candiani M, Calia C and Vignali M (1999) Effects of 3 month therapy with danazol after laparoscopic surgery for stage III/IV endometriosis: a randomized study. Hum Reprod 14,1335–1337.

Blumenfeld Z (2004) Hormonal suppressive therapy for endometriosis may not improve patient health. Fertil Steril 81,487–492.

Busacca M, Marana R, Caruana P, Candiani M, Muzii L, Calia C and Bianchi S (1999) Recurrence of ovarian endometrioma after laparoscopic excision. Am J Obstet Gynecol 180,519–523.

Busacca M, Somigliana E, Bianchi S, De Marinis S, Calia C, Candiani M and Vignali M (2001) Post-operative GnRH analogue treatment after conservative surgery for symptomatic endometriosis stage III-IV: a randomized controlled trial. Hum Reprod 16,2399–2402.

Exacoustos C, Zupi E, Carusotti C, Rinaldo D, Marconi D, Lanzi G and Arduini D (2003) Staging of pelvic endometriosis: role of sonographic appearance in determining extension of disease and modulating surgical approach. J Am Assoc Gynecol Laparosc 10,378–382.

Ghezzi F, Beretta P, Franchi M, Parissis M and Bolis P (2001) Recurrence of ovarian endometriosis and anatomical location of the primary lesion. Fertil Steril 75,136–140.

Giudice LC and Kao LC (2004) Endometriosis. Lancet 364,1789–1799.

Jones KD and Sutton CJ (2000) Laparoscopic management of ovarian endometriomas: a critical review of current practice. Curr Opin Obstet Gynecol 12,309–315.

Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, Hummelshoj L, Prentice A and Saridogan E (2005) ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod 20,2698–2704.

Muzii L, Marana R, Caruana P and Mancuso S (1996) The impact of preoperative gonadotropin-releasing hormone agonist treatment on laparoscopic excision of ovarian endometriotic cysts. Fertil Steril 65,1235–1237.

Muzii L, Marana R, Caruana P, Catalano GF, Margutti F and Panici PB (2000) Postoperative administration of monophasic combined oral contraceptives after laparoscopic treatment of ovarian endometriomas: a prospective, randomized trial. Am J Obstet Gynecol 183,588–592.

Nishida M, Watanabe K, Sato N and Ichikawa Y (2000) Malignant transformation of ovarian endometriosis. Gynecol Obstet Invest 50 (Suppl. 1), 18–25.

Redwine DB (1999) Ovarian endometirosis: a marker for more extensive pelvic and intestinal disease. Fertil Steril 72,310–315.

Saleh A and Tulandi T (1999) Reoperation after laparoscopic treatment of ovarian endometriomas by excision and by fenestration. Fertil Steril 72,322–324.

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