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CLINICAL ARTICLE

Clinical and histopathologic predictors of reoperation due to recurrence of leiomyoma after laparotomic myomectomy

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ABSTRACT

Objective: To assess clinical and histopathologic risk factors for reoperation after laparotomic myomectomy due to leiomyoma recurrence. *Methods:* A case–control study was conducted of patients who underwent their first myomectomy for leiomyoma without receiving gonadotropin-releasing hormone analogues at Ankara University School of Medicine, Ankara, Turkey, between January 2000 and December 2004. Medical records and histopathologic samples were reviewed, and participants completed a telephone interview. Patients in the case group had undergone reoperation within 5 years; those in the control group had not required further surgery. *Results:* There were 51 patients in the case group and 61 controls. The number of women who had given birth after the index surgery was lower among cases than controls (4 [7.8%] vs 13 [21.3%]; $P = 0.048$), as was the median size of the largest leiomyoma removed (4 cm [range 3–10] vs 5 cm [range 3–25]; $P = 0.009$). Reoperation was more likely among patients aged at least 40 years at index surgery (OR 1.10; 95% CI 1.18–7.78; $P = 0.021$) and those with myxoid change (OR 2.04; 95% CI 1.07–55.41; $P = 0.043$). The number of leiomyomas removed was negatively associated with reoperation (OR 0.30; 95% CI 0.58–0.93; $P = 0.012$). *Conclusion:* Young age, removal of many or large leiomyomas, and pregnancy after myomectomy decreased reoperation risk, whereas myxoid change increased risk.

1. Introduction

Hysterectomy is the most widely used and definitive treatment for uterine leiomyomas (fibroids). However, myomectomy is an alternative option that provides excellent symptomatic relief, with the advantage of sparing fertility [1]. Although the aim of myomectomy is to completely ablate leiomyomas from the uterus, recurrence remains a potential risk associated with the use of this procedure.

Different theories have been put forward to explain the recurrence of leiomyoma after myomectomy. First, the growth of small residual leiomyomas missed during surgery could lead to recurrence [2]. Second, the natural evolution of a myometrial disease might be responsible for both the initiation and continued proliferation of leiomyomas [3]. Nevertheless, not all myomectomies will result in recurrence.

Previous studies used various indicators to diagnose recurrence, such as functional signs (menorrhagia and pelvic pain), systematic ultrasonographic investigation at regular intervals, clinical examination with oriented ultrasonography, and the use of retrospective questionnaires [4]. However, methodological discrepancies between these studies resulted in different recurrence rates. Recurrence after myomectomy has been reported to affect 4.8%–55.6% of patients, with rates of subsequent reoperation and hysterectomy of 0.0%–31.6% and 0.0%–28.6%, respectively [4].

Age, number of leiomyomas, size of the uterus, type of surgical procedure, use of medical therapies such as gonadotropin-releasing hormone (GnRH) analogues, and parity after myomectomy are all known to influence rates of recurrence [4]. Although previous studies have examined the clinical risk factors associated with recurrence of leiomyoma, there has been little evaluation of the histopathologic predictors [4–7].

The aims of the present study were, therefore, to assess clinical and histopathologic risk factors of reoperation within 5 years of laparotomic myomectomy due to recurrence of leiomyoma and determine risk factors associated with the need for multiple reoperations.

2. Materials and methods

A case–control study was conducted among patients who had undergone myomectomy for leiomyoma in the gynecology clinic of the Department of Obstetrics and Gynecology at Ankara University School of Medicine, Ankara, Turkey, between January 1, 2000, and December 31, 2004. To be included in the present study, patients had to have undergone their first myomectomy (index surgery) at the study center,

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before which GnRH analogues had not been administered. Exclusion criteria were the presence of any systemic disease, the detection of any pathology other than leiomyoma, and no examination by a gynecologist within the year before analysis. Additionally, patients who could not be reached by telephone or who were not willing to participate were excluded. The present study was approved by the institutional review board of Ankara University School of Medicine.

Demographic variables (age, parity, presence of symptoms, family history of cancer, and phase of the menstrual cycle) and surgical variables (number of leiomyomas removed and size of the largest leiomyoma) were recorded in the medical record at the time of index surgery. During the telephone interview for the present study, patients were asked about abnormal uterine bleeding or pelvic pain, determination of leiomyoma recurrence during routine gynecologic examinations, parity since the index surgery, and the need for reoperation (myomectomy or hysterectomy) owing to recurrence of leiomyoma.

The case group comprised patients who had undergone reoperation within 5 years of the index surgery due to recurrence of leiomyoma; patients in the control group had not required further surgery. Leiomyoma recurrence in the case group was defined by recurrent symptoms and/or ultrasonographic features. In the case group, women who had undergone multiple reoperations (i.e.at least two procedures owing to recurrence of leiomyoma) were also evaluated separately.

The histopathology slides from the index surgeries were re-evaluated microscopically by a gynecologic pathologist (D.K.). For each patient, all the enucleated leiomyomas were assessed. Tumors with five to 15 mitotic figures per 10 high-power fields were defined as mitotically active leiomyomas. Tumors with focal or diffuse epithelioid differentiation were defined as leiomyomas with epithelioid differentiation, whereas tumors with moderate-to-severe atypia without accompanying high mitotic count or necrosis were defined as atypical leiomyomas. Tumors with highly cellular areas were defined as cellular leiomyomas. All these subtypes were classified as non-ordinary leiomyomas; tumors without these specific morphological features were classified as classic leiomyomas. Furthermore, the presence of hyaline degeneration, necrosis (ischemic or coagulation), or myxoid change were also noted.

The data were analyzed using SPSS version 15.0 (SPSS Inc, Chicago, IL, USA). The Shapiro–Wilk test was used to test distribution of normality; the results suggested that the use of non-parametric tests was most appropriate for the present analysis. Between-group differences were analyzed using χ^2 or Fisher exact tests for categorical variables. Continuous variables were evaluated using the Mann–Whitney U test. Multivariate logistic regression analysis with a model-building strategy was used as previously described [8] to identify factors predictive of the outcome variables. $P < 0.05$ was considered statistically significant.

3. Results

Overall, 208 patients were assessed for eligibility using their hospital records. All the patients were white and premenopausal. Overall, 38 patients could not be reached by telephone, 13 were unwilling to participate, and 44 had not undergone a gynecologic examination in the year before analysis. One patient was excluded because of misdiagnosis during index surgery; this patient was re-diagnosed with epithelioid leiomyosarcoma. Consequently, 112 patients were included in the present study, 51 of whom had undergone reoperation within 5 years (case group). Additionally, 10 women had undergone multiple reoperations.

No significant between-group differences were identified for median age at index surgery, median parity before the index surgery, presence of any symptoms, presence of any other diseases (diabetes mellitus, hypertension, cardiovascular disease, or thyroid dysfunction), family history of cancer, multiple leiomyomas, and median number of leiomyomas removed (Table 1). However, fewer women in the case group than the control group had given birth after the index surgery ($P = 0.048$) (Table 1). The median size of the largest leiomyoma removed was also lower in the case group than in the control group ($P = 0.009$) (Table 1).

Table 1
Clinical and surgical variables.[a]

Variable	Reoperation (n = 51)	No reoperation (n = 61)	P value
Age at index surgery, y	40 (26–55)	38 (24–45)	0.08
Parity before index surgery	0 (0–9)	0 (0–5)	0.89
Presence of any symptoms[b]	35 (68.6)	40 (65.6)	0.51
Presence of additional disease[c]	12 (23.5)	14 (23.0)	0.85
Family history of cancer	8 (15.7)	11 (18.0)	0.81
Parity after index surgery	4 (7.8)	13 (21.3)	0.048
Presence of multiple leiomyomas	24 (47.0)	37 (60.6)	0.14
Leiomyomas removed at index surgery	1 (1–5)	2 (1–16)	0.08
Size of largest leiomyoma at index surgery, cm	4 (3–10)	5 (3–25)	0.009

[a] Values given as median (range) or number (percentage), unless indicated otherwise.
[b] Abnormal uterine bleeding, pelvic pain, constipation, or urgency.
[c] Diabetes mellitus, hypertension, cardiovascular disease, or thyroid dysfunction.

Re-evaluation of histopathology slides from the index surgeries was not possible for eight patients (three in the case group and five in the control group) because the histopathologic slides from the index surgery were missing. Hence, the analysis of pathologic variables included 104 patients. In all, 28 non-ordinary leiomyomas were identified in the cohort, comprising 16 cellular leiomyomas, eight mitotically active leiomyomas, three leiomyomas with epithelioid differentiation, and one atypical leiomyoma. No difference was detected in the numbers of patients with each type of non-ordinary leiomyoma who had to undergo reoperation (Table 2). Furthermore, no between-group differences were identified for hyaline degeneration, myxoid change, and the presence of ischemic necrosis (Table 2).

Histopathologic parameters were also evaluated among the 10 patients who underwent multiple reoperations versus the 94 patients without multiple reoperations. The rates of epithelioid differentiation and non-ordinary leiomyomas were significantly increased among patients with multiple reoperations versus patients without multiple reoperations ($P = 0.024$ and $P = 0.027$, respectively) (Table 3).

The multivariate logistic regression analysis showed that women aged 40 years or older during the index surgery had an increased risk of reoperation within 5 years ($P = 0.021$) (Table 4). Myxoid change also increased the risk of reoperation ($P = 0.043$) (Table 4). By contrast, the risk of reoperation within 5 years decreased with increasing number of leiomyomas removed ($P = 0.012$) (Table 4).

4. Discussion

The present study found that age (≥40 years) and myxoid change were associated with increased risk of reoperation within 5 years of the index surgery for leiomyoma. Conversely, the number of leiomyomas removed showed an inverse correlation with reoperation risk. The number of women who had given birth after the index surgery

Table 2
Histopathologic variables.[a]

Variable	Reoperation (n = 48)	No reoperation (n = 56)	P value
Non-ordinary leiomyoma	14 (29.2)	14 (25.0)	0.63
Mitotically active	4 (8.3)	4 (7.1)	0.82
Epithelioid differentiation	2 (4.2)	1 (1.8)	0.47
Atypical leiomyoma	1 (2.1)	0	0.27
Cellular leiomyoma	7 (14.5)	9 (16.1)	0.83
Hyaline degeneration	21 (43.8)	28 (50.0)	0.52
Ischemic necrosis	3 (6.3)	5 (8.9)	0.60
Myxoid change	6 (12.5)	2 (3.6)	0.08

[a] Values given as number (percentage) unless indicated otherwise.