RESEARCH ARTICLE

Effect of pregnancy on recurrence of symptomatic uterine myomas in women who underwent myomectomy

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Abstract

Background: There is no consensus in the literature regarding risk factors associated with recurrence of uterine leiomyomas. In this study, we evaluated the factors that affect the recurrence of uterine leiomyomas in women who underwent laparotomic or endoscopic myomectomy.

Methods: This retrospective study included 378 patients that underwent myomectomy. Patient follow-up ranged from two to eight years, and they were classified according to the recurrence of myoma uteri. Age, gravidity, parity, presenting complaints, prior surgery, comorbidity, smoking status, intraoperative and postoperative features, and Ca 125 levels were obtained from the hospital records and patient files.

Results: Recurrence was detected in 67 women (17.72 %). No statistically significant differences were observed in the demographic data and past obstetric history between the recurrent and non-recurrent groups. The number of myomas was higher in the recurrence group as compared to the non-recurrence group [2 (range: 1-41) vs 1 (1-19), respectively, p =0.022]. Pregnancy rates were statistically higher in the recurrence group as compared to the non- recurrence group (17.9 % vs 7.1 %, respectively, p =0.005). Pregnancy after myomectomy increased the risk of recurrence by 2.8-fold (odds ratio: 2.87; 95 % confidence interval: 1.34-6.13). No significant differences were observed between the two groups regarding the surgical route, fibroid size, uterine location, and position of the myomas in the uterus.

Conclusion: Women who had more than two myomas should be informed of the possibility of recurrent myoma uteri. Additionally, pregnancy in women who previously had a myomectomy was found to be a risk factor for recurrence of the uterine myoma. HIPPOKRATIA 2018, 22(3): 122-126.

Keywords: Uterine myomas, myoma uteri, fibroid, recurrence, risk factors, pregnancy

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Introduction

Uterine myoma is the most common type of neoplasm in the uterus, with 25-30 % of women having complaints about this condition[1]. Of these women, 50 % are symptomatic and have vaginal bleeding, pelvic pain, pressure sensation, severe anemia, and/or urethral obstruction[2,3]. The treatment modalities of myoma uteri include hysterectomy and myomectomy.

Myomectomy is the primary treatment modality for uterine leiomyoma in women who wish to protect their fertility[4]. Although laparotomic myomectomy is still frequently performed for uterine myomas, laparoscopic myomectomy has become the gold standard of treatment[5]. Previous studies reported factors of recurrence in women who underwent myomectomy, with a rate of repeat myomectomy and hysterectomy up to 31.6 % and 28.6 %, respectively[6-8]. In particular, the effect of pregnancy on the recurrence of uterine myoma after myomectomy is not clear. Nevertheless, there is a paucity of standardized evidence for clinicians seeking guidance to inform this group of women when they consider their fertility chances.

Due to the lack of consensus, we aimed to readdress the potential risk factors for symptomatic myomas in the current era of minimally invasive surgery, as laparoscopic myomectomy is now considered the best option for treating symptomatic fibroids in women who wish to retain fertility. In this context, we aimed to evaluate the relationship of recurrent myoma with certain demographic, laboratory, and surgical features.

Methods

This retrospective study included data of patients who underwent myomectomy between January 2008 and December 2013 at the Zekai Tahir Burak Women's Health Research and Education Hospital, in Ankara, Turkey, which is a referral medical center in the middle region of Turkey. All cases were followed up for at least two (4.4 ± 1.2) years, and the recurrence rate was evaluated at the end of 2016. Data were collected from hospital records and patient files; patient characteristics and demographics were analyzed descriptive-

ly. Recorded risk factors included age, gravidity, parity, presenting complaint, previous surgery, comorbidity, smoking status, intraoperative and postoperative features, and Ca 125 values. The study was approved by the institutional review board (No: 26, date: 26/3/2018) and was performed according to the standards of the Helsinki Declaration. All consecutive patients who underwent myomectomy during the study period were included in this retrospective trial.

The diagnosis of uterine myoma was confirmed by histopathologic reports of the specimens. The majority of the patients attended follow-up visits every 6-12 months after surgery and had an ultrasonographic examination at each visit. Data from patients who did not attend follow-up visits were obtained by telephone, and these patients were invited to our outpatient clinic to have a new ultrasound control. All the patients who did not attend follow-up visits were directly questioned whether they had additional surgical interventions at another hospital. Re-examinations were performed in the early follicular phase with the use of similarly featured transvaginal ultrasound devices. The pregnancy status following myomectomy was also re-evaluated for each woman. Exclusion criteria were as follows: use of oral anti-diabetic agents and corticosteroids or a history of chronic inflammatory endocrine and metabolic diseases. Patients were also excluded from the study if they were submitted to a hysterectomy for an indication other than uterine myoma, had no clinical follow-up or could not be reached by phone, received hormonal contraceptive treatment, had pelvic surgery for other reasons after the index surgery, and received interventional radiological treatment for myomas. Recurrence was defined as the presence of a uterine myoma larger than two cm in diameter detected during an ultrasonographic examination.

The surgical technique used for abdominal and laparoscopic procedures was performed as previously reported[9]. Uterine leiomyomas were resected by a monopolar resectoscope in patients with submucosal myomas, as previously defined[10]. Expert gynecological surgeons with adequate surgical experience performed all the surgical procedures.

Statistics

Statistical analyses were performed using the IBM SPSS statistics for Windows, Version 21.0, (IBM SPSS, IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess normal distribution characteristics of the data. Continuous and normally distributed variables are presented as mean ± standard deviations, and intra-group differences were investigated using the Student's t-test. Continuous variables with non-normal distribution are expressed as median (minimum-maximum), and differences between variables were analyzed using the Mann-Whitney U test. Categorical variables are expressed as percentages. Differences between categorical data were evaluated using the chi-square (χ^2) test. Two-sided p values were considered statistically significant at $p < 0.05$.

Results

During the study period, 489 myomectomies were performed in our hospital, and 111 women were excluded from the final analysis due to incomplete data or/and lack of follow-up. The present study finally included a total of 378 patients who had undergone myomectomy and attended follow-up examinations at our center. Patients were classified according to the recurrence of myoma uteri. The demographic and clinical characteristics of the patients in both groups are shown in Table 1. The mean age was 37.4 ± 5.0 years in the recurrent group and 36.6 ± 5.7 years in the non-recurrent group (p =0.229). The groups were also comparable in terms of body mass index (BMI), gravidity, and parity (p =0.827, p =0.543, and p= 0.345, respectively).

The median follow-up time was 3.5 (range: 2-8) years. Sixty-seven out of the 378 women (17.7 %) experienced recurrent myoma uteri while the remainder 311 subjects (82.3 %) did not. The recurrence interval was found to be 20.0 ± 11.6 months. No significant differences were observed between the recurrent and non-recurrent groups regarding surgical indications such as pelvic pain, menometrorrhagia, and infertility (p =0.926). The abdominal route was the most commonly used myomectomy method in both groups. Preoperative CA 125 concentrations, preoperative and postoperative hemoglobin/hematocrit, and the need for blood transfusion were similar between the two groups (Table 2). Presence of co-morbid diseases, history of previous pelvic surgery, and smoking status of the patients were also similar in the recurrent and non-recurrent groups. The mean size of the dominant fibroid was 7.0 ± 3.5 cm and 6.3 ± 2.3 cm in the recurrent and non-recurrent group, respectively (p =0.239). The number of myomas was higher in the recurrent than the non-recurrent group [2 (range: 1-41) and 1 (1-19), respectively; p =0.022]. However, uterine location and the myometrial placement of myomas was not significantly different between the groups. Recurrence rates were statistically higher in women who became pregnant after a myomectomy as compared to women who did not (17.9 % and 7.1 %, respectively; p =0.005). Pregnancy after myomectomy increased the risk of recurrence by 2.8-fold (odds ratio: 2.87; 95 % confidence interval: 1.34- 6.13).

Discussion

In the current study, women who underwent myomectomy in our clinic were retrospectively reviewed. The clinical and demographic characteristics of the patients who developed a recurrence during the postoperative follow-up were compared with those who had no recurrence. Thus, we evaluated the potential risk factors involved in the development of a recurrence.

Epidemiological studies have shown that the rate of myomas in nulliparous women is higher than in multiparous women. This difference was attributed to either reduced fertility in conjunction with myoma presence or to the protective effect of pregnancy on the development of leiomyoma. Similarly, Hanafi et al[11] stated that subsequent parity is associated with a lower probability of recurrence, but the cause and effect relationship between these two variables is unclear. Contrary to previously published studies, the results of our study revealed that recurrence rates increased in women

Table 1: Comparison of the demographic characteristics of the 378 enrolled women classified into the recurrent (n: 67) and non-recurrent (n: 311) groups.

Variables	Recurrence (n: 67)	No recurrence (n: 311)	p
Age (years)	37.4 ± 5.0	36.6 ± 5.7	0.229
BMI (kg/m^2)	27.4 ± 4.1	27.5 ± 4.1	0.827
Gravidity	2 (0-5)	2 (0-8)	0.503
Parity	1 (0-5)	1 (0-6)	0.345
Multiparity	44 (65.7)	180 (57.9)	0.239
Number of live children	1 (0-6)	1 (0-4)	0.696
Number of miscarriages	0 (0-4)	0 (0-4)	0.499
Initial complaint			
Pelvic pain	28 (41.8)	123 (39.5)	
Pelvic pressure	0	3 (1)	
Asymptomatic	6 (9)	32 (10.3)	0.926
Menometrorrhagia	25 (37.3)	106 (34.1)	
Infertility	7 (10.4)	42 (13.5)	
Habitual abortion	1 (1.5)	5 (1.6)	
Previous surgery	17 (25.4)	102 (32.8)	0.235
Comorbidity	10 (14.9)	9 (9.0)	0.144
Smoker	11 (16.4)	65 (20.9)	0.406
Additional gynecologic pathology	23 (34.4)	91 (29.3)	0.412
Pregnancy	12 (17.9)	22 (7.1)	0.005
Time to recurrence (months)	20.0 ± 11.6 17 (7-48)		

Data are expressed as mean ± standard deviation, median (range in brackets), or number of patients (percentage in brackets). A p value <0.05 is considered statistically significant. BMI: Body mass index, n: number of patients.

Table 2: Laboratory parameters and operative findings of the 378 enrolled women classified into the recurrent (n: 67) and non-recurrent (n: 311) groups.

Variables	Recurrence (n: 67)	No recurrence (n: 311)	p
Preoperative Hb (g/dl)	12.2 ± 1.6	12.3 ± 1.8	0.783
Anemia prevalence	12 (17.9)	62 (19.9)	0.705
Need for blood tx	8 (11.9)	40 (12.9)	0.837
Ca-125 (mU/mL)	30.6 ± 34.2	26.2 ± 16.2	0.934
Operation route			0.802
L/T	63 (94)	287 (92.3)	
L/S	3 (4.5)	15 (4.8)	
H/S	1 (1.5)	9 (2.9)	
Size of myoma (cm)	7.0 ± 3.5	6.3 ± 2.3	0.239
Number of myomas	2 (1-21)	1 (1-19)	0.022
Uterine location			0.185
Anterior	94 (30.2)	32 (47.8)	
Posterior	102 (32.8)	15 (22.4)	
Fundus	42 (13.5)	6 (9.0)	
Intraligamentary	3 (1.0)	1 (1.5)	
Mixed	55 (17.7)	9 (13.4)	
Lateral	11 (3.5)	3 (4.5)	
Cervicovaginal	4 (1.3)	1 (1.5)	
Position in the uterus			0.764
Intramural	194 (62.4)	44 (65.7)	
Intraligamentary	3 (1.0)	1 (1.5)	
Mixed	49 (15.8)	8 (11.9)	
Subserous	53 (17.0)	13 (19.4)	
Submucous	12 (3.9)	1 (1.5)	

Data are expressed as mean ± standard deviation, median (range in brackets), or number of patients (percentage in brackets). A p value <0.05 is considered statistically significant. BMI: Body mass index, n: number of patients. Hb: hemoglobin, tx: transfusion, Ca-125: cancer antigen 125, L/T: laparotomy, L/S: laparoscopy, H/S: hysteroscopy.

who became pregnant after myomectomy[12-14]. In one of the few studies in the literature with consistent results with our study, Stewart et al[7] showed that pregnancy increased recurrence and the associated need for surgery after myomectomy.

Concentrations of steroid hormones (especially estrogens and progesterone) and growth factors play a vital role in the development and overgrowth of uterine myomas. The association of early menarche (before the eleventh year of age) and myoma development may be explained by an increased mitosis rate that increases the probability of genetic mutation in myometrial cells, which is likely due to the extension of the female reproductive age. Sex steroids and growth factors control myometrial proliferation[7,11]. Even anovulatory women, who are characterized by an increased and prolonged estrogen production, may develop myomas[15]. The incidence of myoma in obese women is high, which is mainly due to the increased aromatase activity caused by obesity[16]. In premenopausal women, especially in cases of obesity, the reduced metabolism of estradiol and its decreased inactive metabolites increase the concentration of estrogens, which contributes to the increased growth of fibroids[17].

Recent evidence shows that estrogen acts primarily to increase cell responsiveness to progesterone, and the number of progesterone receptors is elevated at the fibroid level[18,19]. Therefore, selective progesterone receptor modulators have started to be used as therapeutic drugs for uterine myomas. The high recurrence rate of myoma after pregnancy can be attributed to the combined effect of increased growth factors in pregnancy as well as promoter effects of increased levels of estrogen and progesterone during pregnancy.

The hormonal and molecular mechanisms involved in the modification of uterine myomas during pregnancy are unclear and challenging to investigate. As women delay their wish to have children, they are more likely to have complications during pregnancy with myomas. These myomas also cause various obstetric complications that may occur in any time during pregnancy. There are limited studies in the literature that address the progression of myomas throughout pregnancy. Moreover, there are very few published studies that evaluated the course of myomas larger than one cm during pregnancy[20,21]. According to a recent systematic review, uterine myomas appear to be subjected to non-linear changes during pregnancy and puerperium (triphasic)[22]; an initial expansion stage in the first trimester, a deceleration and stabilization phase in the second trimester, and regression in the third trimester and puerperium. Of course, these changes vary in a patient-tailored manner. In particular, adequate evidence demonstrates that fibroids systematically expand in the first trimester of pregnancy. Nevertheless, there is little evidence that fibroids change in the second and third trimester or during the pregnancy and the puerperium.

The remarkable growth of myomas in the first trimester may be related to pregnancy hormones other than sex steroids. Maternal serum estrogen and progesterone levels are higher in the second half of pregnancy compared to the first half. The most recent hypothesis explaining this paradox is attributed to the increased serum human chorionic gonadotropin (hCG) levels in early pregnancy (LH-hCG myomal receptors hyperstimulation theory)[20]. This notion is supported by a recent clinical study showing a statistical correlation between the volumetric expansion of myomas and the logarithmic increase in hCG levels in the first trimester of pregnancy. Similarly, in vitro studies found that exposure of leiomyomal cells to exponentially increasing hCG concentrations leads to dramatic hypertrophic and hyperplastic changes with a gradual decrease in alterations as the duration of the culture increases[23]. However, given the possible histological heterogeneity of myomas in terms of smooth muscle cells and collagen matrix percentages, the expression of luteinizing hormone (LH) receptors is different from myoma to myoma, resulting in a wide range of susceptibilities to hCG stimulation. Apart from the hCG stimulation hypothesis, other hormones secreted by maternal and feto-placental compartments, enzymes, and growth factors also increase significantly, particularly in the early period of pregnancy. Since the potential effects of these substances have not been systematically investigated, the fact that such molecules could have a simultaneous effect on the growth of uterine myomas cannot be ignored.

In this study, there was a direct relationship between the number of myomas that were removed during surgery and recurrence. This finding is akin to previous studies. Nevertheless, Reed et al[15] found no relationship between the number of myomas and recurrence in their study of 628 patients. Whether an inheritance pattern exists is still controversial. If a patient with a myoma has a relative with a myoma in the family, the incidence of myomas is reported to be higher than those without such a relative with a myoma[12]. We did not evaluate this relationship, because many women may be asymptomatic.

The fibroid recurrence rate of 17.7 % detected in our study was significantly lower than the recurrence rates of 21 % and 47.7 % reported by Obed et al[12] and Fedele et al[13], respectively. However, our recurrence rate is higher than that reported by Candiani et al[14] (13.5 %). These differences may be attributed to the different ultrasonographic methods used for diagnosing recurrence. In the current study, we used a combined clinical examination and ultrasonography as a diagnostic method. The same approach had also been used for the preoperative diagnosis. A lower threshold for recurrence (myoma of one cm in diameter) could infer a higher recurrence rate, as suggested by Fedele et al[13].

We surmise that clinical signs and symptoms should not be solely used for diagnosing recurrence at patient's follow-up evaluations. Because myoma symptoms are not specific; thus myomas that develop at different locations after recurrence could cause different symptoms. Some authors investigating myoma recurrence suggested that recurrence may be dependent on myomas that are missed in the initial operation due to their small size. However, many published studies have excluded this condition with careful preoperative ultrasonographic examination. Equally, recurrence can also occur as a natural evolution of myometrial disease as cells undergoing spontaneous chromosomal rearrangements may be responsible for the initiation and proliferation of myoma cells[18].

Consistent with our study, previous studies demonstrated that recurrence could occur in different locations irrespective of time. However, it is possible that, depending on the surgical technique, a myoma smaller than 0.5 cm in size that is developing at the time of the operation cannot be removed. This sometimes can be observed during the examination of hysterectomy materials. During the postoperative pathological examination of the hysterectomy material, microscopic myomas and visually detected small fibroids may be present.

The major limitation of this study is its retrospective nature. Additionally, data from a single institution may not be representative of the general population. A longer follow-up period may result in a higher probability of detecting recurrence. Therefore, the limited follow-up period may have also caused pregnancy rates to be lower in our study. Although our study population was within reproductive age, the mean age was higher as compared to similar studies. However, the inclusion of a relatively high number of patients is the strength of this study.

In this retrospective cohort study, we evaluated the risk factors of women who had undergone myomectomy and diagnosed with a recurrence of myoma uteri. Risk factors that were not statistically different in the recurrent group were age, gravidity, parity, BMI, presenting symptom, laboratory parameters (hemoglobin and Ca 125), operation route, comorbidity, history of pelvic surgery, smoking status, and fibroid size and location. However, the number of myomas (>2) was a significant risk factor of myoma uteri recurrence. Pregnancy was also found to be a contributing factor of uterine myoma recurrence. Additional studies should be performed to investigate the effect of uterine myoma characteristics (size, location, and position) and patient characteristics (ethnicity and parity) on the recurrence of myomas. In addition, more extensive prospective studies are needed to evaluate the effects of pregnancy on recurrence rates after myomectomy.

Conflict of interest

Authors declare no conflict of interest.

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