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Differences in clinical characteristics for the determination of adenomyosis coexisting with leiomyomas

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Abstract

Aim: The objective of the analysis was to determine the characteristics that distinguish women with adenomyosis and leiomyomas from those with leiomyoma only from a sample who underwent hysterectomy for benign uterine diseases.

Methods: This retrospective study was based on the analysis of medical records of 75 women with both adenomyosis and uterine leiomyomas and 218 women with leiomyomas only, diagnosed by histologic analysis of uterine specimens.

Results: Results of multivariate logistic regression analyses showed that women with both adenomyosis and leiomyomas had a higher gravity (odds ratio [OR] 1.16, 95% confidence interval [CI] 1.01–1.33) and more frequent pelvic pain (OR 0.38, 95% CI 0.21–0.7) compared with women with leiomyomas only. Postmenopausal bleeding was commonly reported in women with adenomyosis and leiomyomas. No significant difference was observed between the two groups in terms of menorrhagia and metrorrhagia and the preoperative diagnosis of prolapse.

Conclusions: The presence of concomitant adenomyosis may cause different clinical symptomatology.

Key words: adenomyosis, hysterectomy, leiomyoma, pelvic pain, risk factors.

Introduction

Adenomyosis uteri, a common benign condition of the uterus, is characterized by the presence of ectopic endometrial glands and stroma within the myometrium.[1] In most patients, a diagnosis of adenomyosis is only made by histological examination of the uterus after hysterectomy. Therefore, the exact incidence of adenomyosis is based on published reports of women who have undergone a hysterectomy.[2] Nevertheless, transvaginal ultrasound and magnetic resonance imaging (MRI) have become commonly used modalities in the preoperative diagnosis of adenomyosis.[3] The presenting symptoms of adenomyosis, such as menorrhagia, chronic pelvic pain and dysmenorrhea, are non-specific, making preoperative diagnosis extremely difficult because the symptoms mimic those of other gynecologic pathologies.[4,5] Advanced age, multiparity, surgical disruptions of the endometrial-myometrial border, hyperestrogenemia, smoking and a history of depression could be considered as risk factors for adenomyosis.[6,7]

Uterine leiomyomas are the most common benign tumor of the uterus in women of reproductive age and may present with a variety of symptoms, including abnormal uterine bleeding, dysmenorrhea, pelvic pressure, dyspareunia, increased urinary frequency or constipation.[8] Both uterine leiomyomas and adenomyosis often coexist in the same uterus; therefore, distinguishing between two conditions with similar symptoms can be problematic.[9,10] The prevalence of concomitant adenomyosis has been reported in the literature to range

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from 15–57%, according to the evaluation of uterine specimens of women with leiomyomas.[6,9,11]

Several minimally invasive surgical interventions for non-invasive treatment as uterine-conserving therapies, including uterine artery embolization and magnetic resonance-guided focused ultrasound surgery, have satisfactory success rates in treating uterine symptomatic leiomyomas.[12,13] However, according to evidence-based guidelines, there is limited success of these treatment modalities in women with the presence of concomitant adenomyosis.[14,15] Therefore, distinguishing between leiomyoma and leiomyoma concomitant with adenomyosis may be required to determine the reasonable treatment modality for satisfactory clinical results.

In this study, we aimed to compare the demographic clinical characteristics of women who underwent hysterectomy with a histopathologic analysis of both leiomyomas and adenomyosis and women who underwent hysterectomy with a histopathologic analysis of leiomyomas only.

Materials and Methods

This retrospective study was based on an analysis of the medical records of all patients that consecutively underwent hysterectomy for benign uterine diseases between November 2011 and December 2014 at Bezmialem Vakif University, Istanbul, Turkey. The ethics committee of our hospital approved this study.

Demographic, clinical and pathological data, including age, body mass index (BMI), gravidity (number of all prior pregnancies: previous miscarriages, ectopic pregnancy, stillbirths and live births), parity, history of abdominal surgery and cesarean section, smoking status, menopausal status, medical history, preoperative hematocrit, preoperative measurement of endometrial thickness and pathologic reports of the specimens were all retrieved from the medical records and/or the centralized computer system. A history of medical conditions, including hypertension, diabetes mellitus, hypercholesterolemia and thyroid disease, was recorded if hospital records confirmed the diagnosis. BMI was calculated as weight (kg) divided by the square of height (m^2). Patients with amenorrhea more than one year since the last menstrual period were considered to be menopausal. The woman was defined as a smoker if she smoked more than one cigarette per day. All patients underwent ultrasound examination and endometrial thickness was measured using transvaginal ultrasonography before surgery.

The diagnosis of an abnormal Pap test was based on the documentation of pathology results. The presence of endometriosis was established by confirmation of histologic examination. Patients with incomplete medical records and with gynecologic cancer diagnosed by pathologic examination were excluded from the study.

Indications for hysterectomy, such as treatment-resistant menorrhagia and metrorrhagia, leiomyoma, abdominal pain, postmenopausal bleeding, uterine prolapse and other indications (e.g. cervical dysplasia), were also determined by medical records. The study group included 75 women with both adenomyosis and uterine leiomyomas and the control group included 218 women with leiomyomas only, according to histologic analysis of uterine specimens. All hysterectomy specimens were examined by three pathologists.

Data were expressed as mean ± standard deviation or number and percentage, as appropriate. Statistical analysis was performed after normality testing (histogram analysis and/or Kolmogorov–Smirnov) using IBM SPSS version 21. The student's *t*-test was used for comparisons of normally distributed variables, and the Mann–Whitney U-test was used for categorical variables. Chi-square and Fisher's exact tests were used to compare the proportion of categorical variables. Multivariable logistic regression models were developed to predict the probability of adenomyosis using variables identified during univariate analysis. Odds ratios (OR) with 95% confidence intervals (CI) were also calculated. $P < 0.05$ was considered statistically significant.

Results

After 33 women were excluded because of incomplete data, the medical records of 453 patients who underwent hysterectomy for benign uterine diseases were analyzed in this study. The details of study design are provided in Figure 1.

The demographic, reproductive and surgical characteristics of the cohort are presented in Table 1. There were no significant differences between groups in terms of their age, BMI, smoking, menopausal status, history of ectopic pregnancy, spontaneous abortions, abdominal surgery and cesarean section, endometrial thickness and preoperative hematocrit. Abnormal Pap smear rates were also similar in each group. Moreover, we observed no differences between the two groups regarding history of hypertension, diabetes mellitus, thyroid disease and hypercholesterolemia. Gravidity and parity were

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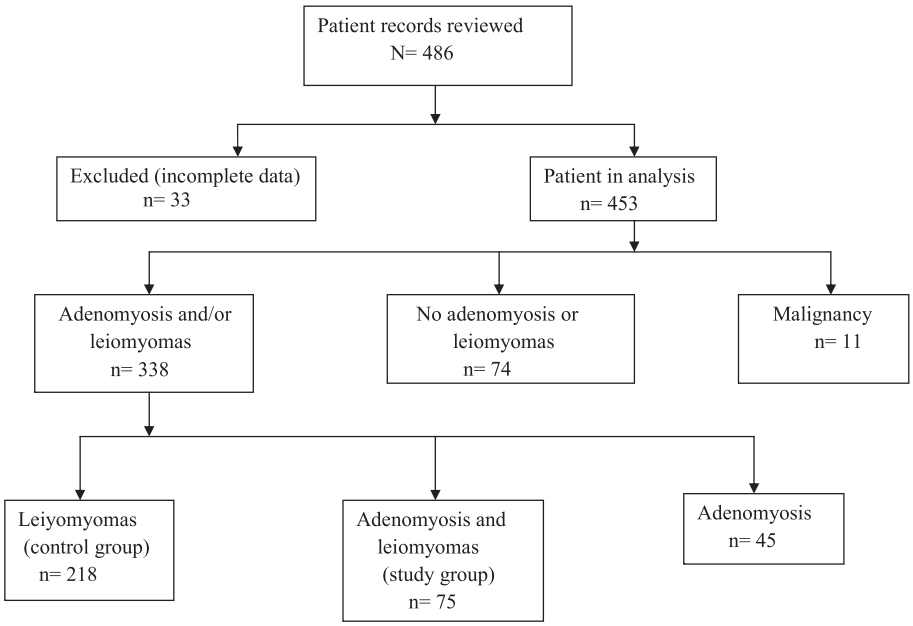

Figure 1 Flowchart for patient selection.

Table 1 The demographic, reproductive and surgical characteristics of the cohort

	Adenomyosis and leiomyomas (n = 75)	Leiomyomas alone (n = 218)	P
Age (years)†	50.35 ± 6.73	49.87 ± 6.83	0.6
Body mass index (kg/m^2)†	30.75 ± 4,69	30.13 ± 3.87	0.26
Gravidity‡	4.41 ± 2.44	3.55 ± 2.12	0.005
Parity, n (%)§			
0	6 (8)	46 (21.1)	0.01
1 or more	69 (92)	172 (78.9)	
History of miscarriage, n (%)§	19 (25.3)	39 (17.9)	0.16
History of ectopic pregnancy, n (%)¶	2 (2.7)	3 (1.4)	0.45
History of cesarean section, n (%)§	8 (10.7)	36 (16.5)	0.22
Previous abdominal surgery, n (%)§	9 (12)	41 (18.8)	0.17
Menopausal status, n (%)§			
Yes	21 (28)	56 (25.7)	0.69
No	54 (72)	162 (74.3)	
Smoking, yes n (%)§	10 (13.3)	31 (14.2)	0.84
Diabetes, yes n (%)§	13 (17.3)	25 (11.5)	0.19
Hypercholesterolemia, yes n (%)¶	4 (5.3)	8 (3.7)	0.53
Hypertension, yes n (%)§	18 (24)	36 (16.5)	0.14
Thyroid disease, yes n (%)¶	2 (2.7)	4 (1.8)	0.66
Endometrial thickness (mm)†	9.43 ± 4.41	8.22 ± 3.88	0.077
Abnormal Pap smear, yes n (%)¶	3 (4)	7 (3.2)	0.75
Preoperative hematocrit†	35.9 ± 4.5	35.4 ± 5.2	0.46
Number of leiomyomas†	3.89 ± 3.67	3.91 ± 3.96	0.9
Diameter of the largest leiomyoma (cm)†	5.44 ± 3.83	5.55 ± 3.71	0.8
Uterine leiomyoma, n (%)§			
<2 cm	14 (18.7)	35 (16.1)	0.6
≥2 cm	61 (81.3)	183 (83.9)	

Data are shown as mean + standard deviation or n (%). †Student's t-test; ‡Mann–Whitney U test; §Pearson chi-squared test; ¶Fisher's exact test.

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significantly higher in women with adenomyosis and leiomyomas than women with leiomyomas alone.

The diagnoses and symptoms of groups included in this study are presented in Table 2. Pelvic pain occurred in 27.6% (n = 20) of women with both adenomyosis and leiomyomas and 19.7% (n = 43) of women with leiomyomas only and was significantly more frequent in women with both adenomyosis and leiomyomas when compared to women with leiomyomas alone (P = 0.03; OR 0.6, 95% CI 0.22–1.65). Postmenopausal bleeding was commonly reported in women with adenomyosis and leiomyomas compared with women with leiomyomas only (P = 0.04; OR 2.32, 95% CI 1.02–5.31). There was no statistically significant difference between the groups in terms of the presence of abnormal uterine bleeding, including menorrhagia and metrorrhagia. Likewise, no significant difference was observed for the preoperative diagnosis of prolapse between the two groups of patients.

Multivariate logistic regression analysis was performed to identify independent variables that provide the best discrimination between the two groups. The final multivariate model included the following: parity, gravidity, pelvic pain and preoperative diagnosis of postmenopausal bleeding and leiomyoma (Table 3). Based on the results of this analysis, women with both adenomyosis and leiomyomas had a higher gravity (OR 1.16, 95% CI 1.01–1.33) and more frequent pelvic pain (OR 0.38, 95% CI 0.21–0.7) compared with women with leiomyomas only.

The comparison of the other gynecologic pathologies detected by postoperative histopathological analysis, including endometrial polyp, endometrial hyperplasia, endometriosis and ovarian cyst is shown in Table 4. There was no statistical difference in terms of the frequency of these gynecologic pathologies between the two groups.

Table 3 Multivariable logistic regression analyses of factors associated with the presence of adenomyosis and leiomyomas

Variable	P	OR (95% CI)
Gravidity	0.03	1.16 (1.01–1.33)
Pelvic pain	0.02	0.38 (0.21–0.7)

CI, confidence interval; OR, adjusted odds ratio.

Discussion

The objective of the analysis was to determine the characteristics that distinguish women with adenomyosis and leiomyomas from those with leiyomyomas only from a sample who underwent hysterectomy for benign uterine diseases.

Although still debated, it was reported that pregnancy-related factors, such as parity, cesarean section and spontaneous or induced abortion are associated with an increased risk of adenomyosis.[7,11,16] On the other hand, some studies have failed to confirm these findings.[6,9] In a recent study, Naftalin *et al*. found that only gravidity remained significant according to the results of multivariate analysis, although BMI, gravidity, parity, previous spontaneous abortion, vaginal delivery and cesarean delivery are associated with adenomyosis by univariate analysis.[4] Likewise, in our study, gravidity was found to be significantly associated with the presence of concomitant adenomyosis based on our multivariate regression model. Furthermore, Taran *et al*. reported that parous women with leiomyomas who underwent hysterectomy were four times more likely to have a concomitant diagnosis of adenomyosis than women with leiomyomas alone.[17]

Although several studies have suggested that a history of laparotomy and prior uterine surgery (such as cesarean delivery, myomectomy, dilation and curettage)

Table 2 Indications for surgery†

	Adenomyosis and leiomyomas, n (%)	Leiomyomas alone, n (%)	P	OR (95% CI)
Menorrhagia	25 (33.3)	88 (40.4)	0.28	0.37 (0.42–1.28)
Metrorrhagia	21 (28)	70 (32.1)	0.51	0.82 (0.46–1.46)
Pelvic pain	20 (26.7)	43 (19.7)	0.03	0.6 (0.22–1.65)
Leiomyoma	23 (30.7)	97 (44.5)	0.04	0.55 (0.31–0.96)
Postmenopausal bleeding	11 (14.7)	15 (6.9)	0.04	2.32 (1.02–5.31)
Uterine prolapse	5 (6.7)	23 (10.6)	0.32	0.6 (0.22–1.65)
Other	5 (6.7)	5 (2.3)	0.07	3.04 (0.85–10.82)

Data are shown as n (%). †Columns do not add to 100% because more than one presentation may be present. CI, confidence interval; OR, odds ratio.

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Table 4 Concomitant gynecologic pathologies found in cases and controls

	Adenomyosis and leiomyomas, *n* (%)	Leiomyomas alone, *n* (%)	*P*
Endometrial polyp†	6 (8)	18 (8.3)	0.94
Endometrial hyperplasia†	4 (5.3)	15 (6.9)	0.63
Endometriosis‡	3 (4)	10 (4.6)	0.83
Ovarian cyst‡	2 (2.7)	11 (5)	0.38

Data are shown as n (%). †Pearson chi-squared test; ‡Fisher's exact test.

were related to an increased risk of adenomyosis, we did not find statistically significant differences in terms of the history of previous cesarean delivery and laparotomy between the two groups.[7,18,19] Hence, our results did not support the hypothesis that surgically-induced endometrial implantation may contribute to the development of adenomyosis.[6]

The majority of women with myomas are asymptomatic, but abnormal uterine bleeding, pelvic pain and pelvic pressure are the most common symptoms associated with fibroids.[20] These symptoms related to uterine myomas are also being seen in adenomyosis.[21] While the relationship between adenomyosis and menorrhagia is still uncertain, a previous prospective observational study showed that there was no significant relationship between the presence of adenomyosis and menorrhagia.[22] Similarly, our results demonstrate that women with both adenomyosis and leiomyomas had no higher incidence of menorrhagia or metrorrhagia compared with women with leiyomyomas alone. On the other hand, previous studies have shown that women with leiomyomas are only slightly more likely to report pelvic pain compared with women without myomas.[23,24] In a recent study, Taran *et al*. reported that pelvic pain is more frequent in women with both adenomyosis and leiomyomas compared women with leiomyomas only.[17] Consistent with this report, we found that women with both adenomyosis and leiomyomas were more likely to experience pelvic pain. Weiss *et al*. attempted to determine the specific symptoms that predict the presence of adenomyosis in women who underwent hysterectomy but did not find a relationship between chronic pelvic pain, abnormal bleeding and adenomyosis; they hypothesized that adenomyosis is actually an incidental finding rather than the cause of symptoms.[9]

Preoperative diagnosis of adenomyosis is poor, ranging from 2.6–26% because of its non-specific clinical presentation.[25] Unfortunately, we were unable to preoperatively detect adenomyosis in our study. Even with the combination of transvaginal ultrasound and MRI to diagnose adenomyosis, a diagnosis remains difficult before surgery.[26]

Adenomyosis, endometriosis and endometrial hyperplasia have been demonstrated to be estrogen-dependent gynecologic diseases.[7,27] Bergholt *et al*. found a significant association between endometrial hyperplasia and adenomyosis.[6] However, Genc *et al*. found no relationship between adenomyosis and endometrial hyperplasia or endometriosis.[28] According to our results, the prevalence of endometriosis, endometrial hyperplasia and endometrial polyps were similar in women with adenomyosis and leiomyomas and with leiomyomas only in hysterectomy specimens.

The present study has several limitations. First, zretrospective review of medical records could preclude objective measurement of the patients' symptoms. Second, a relatively small sample size of hysterectomy cases was analyzed. Third, all pathology specimens were not examined by the same pathologist because the postoperative identification of adenomyosis is based on pathologist's awareness and may be difficult because of a lack of consensus of diagnostic criteria for adenomyosis.[16]

In conclusion, women with histological diagnoses of both adenomyosis and leiomyomas have a higher gravity and more frequent pelvic pain compared to women with leiomyomas alone. The presence of concomitant adenomyosis may cause different clinical symptomatology. Further prospective studies are required in order to confirm our findings.

Disclosure

The authors have no conflict of interest.

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