Gynecology; *and Gynecological Oncology*

Prevalence of Asymptomatic Uterine Leiomyoma in Western Türkiye and Factors Affecting Myoma Presence

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ABSTRACT

OBJECTIVE: To reveal the prevalence of asymptomatic uterine leiomyomas among gynecologic patients and to evaluate risk factors associated with the presence of leiomyomas.

STUDY DESIGN: Two thousand five hundred eighty-three patients aged between 18 and 66 years who presented to the gynecology outpatient clinic of our hospital in January and February 2021 who had an intact uterus and underwent transvaginal ultrasound were included in the study. Patients withsymptoms due to fibroids were defined as symptomatic, and those without symptomswere defined as asymptomatic; then two groups were compared in terms of certain variables.The independent risk factors associated with the presence of fibroids were determined using univariate and multivariate logistic regression analysis.

RESULTS: Leiomyomas were detected in a total of 437 patients with an overall prevalence of 17.2%. Leiomyomas were detected in 12.2% of asymptomatic patients and 27.8% of symptomatic patients (p<0.001). The prevalence of fibroids tended to increase with advancing age and decreased after age 50 years. It was observed that myoma diameter was significantly large (29.5 (6-123) mm and 18 (7-74) mm; p<0.001) and the frequency of multiple myomas was significantly high in symptomatic patients (46.5% vs. 33.6%; p<0.001). In the multivariate logistic regression analysis, high body mass index, younger age at menarche, and not using oral contraceptives were associated with the presence of fibroids.

CONCLUSION: Approximately half of all leiomyomas, one of the important gynecological health problems of women, are asymptomatic.

Keywords: Diagnosis, Leiomyoma, Prevalence

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Introduction

Uterine leiomyomas (also known as myomas, or fibroids) are the most common pelvic tumors in women of reproductive age (1).These monoclonal tumors, arising from a mutation of a single myometrial somatic stem cell, are characterized by excessive production of extracellular matrix (ECM) (2). Leiomyomas are extremely rare before menarche, their prevalence increases with age in the reproductive period, and regresses after menopause. Thus, fibroids appear to develop and grow in response to ovarian steroids (3).

There are insufficient data on the prevalence of uterine fibroids in Türkiye. Worldwide prevalenceestimates vary from 4.5% to 68.6%, depending on the study population and diagnostic methodology (4). Multiple risk factors have been identified for the development of fibroids. The Black/African-Americanrace is the only factor consistently shown to be associated with increased risk (4). Other risk factors are age, obesity, nulliparity, endogenous and exogenous hormonal factors, family history of fibroids, and lifestyle (diet, caffeine consumption, physical activity, and smoking) (5,6). Although it is a common disease, the pathophysiology is not fully understood. Data suggest that estrogen acts mainly by increasing the cell response to progesterone, and progesterone and its receptor are essential for tumor growth (3,7). Accumulating evidence sug-

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gests that alterations in several genes, protooncogenes, and epigenetic mechanisms may play an important role in the initiation of fibroids, rather than hormonal factors alone (8).

Myomas do not have specific clinical findings, their manifestations are heterogeneous according to their size and location. The most common symptom is heavy menstrual bleeding. Prolonged menstrual bleeding and intermenstrual bleeding may also be presenting symptoms. Non-cyclic pain, abdominal protuberance, dyspareunia, and pelvic pressure, bladder or bowel dysfunction resulting in urinary incontinence or retention, constipation are symptoms of bulkyuterine fibroids (9,10). Impaired fertility, recurrent pregnancy loss, and adverse obstetric outcomes are reproductive problems that can be seen in patients with fibroids (11,12).

In this study, we aimed to reveal the prevalence of asymptomatic leiomyomas in our female populationbecause data on the prevalence of leiomyomas in Türkiye are limited and a gap is possible in the estimation of asymptomatic patients. The secondary objective was to evaluate risk factors associated with the presence of leiomyomas.

Material and Method

This cross-sectional study was performed in an education and research hospital, after obtaining approval from the local ethics committee (2011-KAEK-25 2021/01-10). The study was conducted in accordance with the Declaration of Helsinki and written informed consent was obtained from all participants. The study population included unselected gynecologic patients who were admitted to our gynecology outpatient clinic between February and April 2021. Virgins, patients who could not tolerate transvaginal ultrasound, patients who had a previous hysterectomy, and pregnant women were excluded from the study.All included patients were Caucasian women. Data regarding age, body mass index (BMI), parity, menarche age, age at first birth, previous uterine surgery, known presence of fibroids, family history of fibroids, comorbidities such as hypertension (HT), diabetes mellitus (DM), and the use of hormonal contraceptivesand smoking were registered.

Heavy or prolonged menstrual bleeding, bulk-related symptoms such as pelvic pressure and pain, and reproductive dysfunction (ie, infertility, miscarriage, obstetric complications) were defined as symptoms suggestive of fibroids (13), and patients with at least one of these symptoms were included in the symptomatic patient group. Patients who did not have the specified symptoms and were admitted for cancer screening, contraception, amenorrhea, oligomenorrhea, hirsutism, and other gynecologic diseases constituted the asymptomatic patient group.

Three experienced radiologists who performed the ultrasound examinations were blinded to the medical history and the symptomatology of the patients. Ultrasound examinations were conducted transvaginally using a GE Health Care Logic S7 Expertscannerusinga high-frequency, high-resolution 5-9-MHz endovaginal probe. Uterine dimensions and structure, endometrial thickness, and adnexal pathologies were assessed, and the number, location, and size of the fibroids were defined. Myoma diameter was calculated by taking the average of the three measured dimensions. The location of the fibroid was defined according to the 2011 International Federation of Gynecology and Obstetrics (FIGO) classification system, FIGO types 0, 1, and 2 fibroids were included in the study as submucosal myomas, FIGO types 3, 4, and 5 were included as intramural myomas, FIGO types 6 and 7 were accepted as subserosal myomas and FIGO type 8 as cervical myomas (14). The location and size of the leading fibroid were taken into consideration in patients with multiple fibroids.

Statistical analysis

Data were analyzed using the IBM SPSS Statistics 18© Copyright SPSS Inc. 1989, 2010 software. The conformity of continuous variables to normal distribution was examined using the Kolmogorov-Smirnov test. Categorical variables in the study are presented with frequency (n) and percentage (%), and continuous variables are presented with median (min-max) values because parametric test assumptions were not met. Pearson's Chi-square, Fisher's Exact, or the Fisher-Freeman-Halton Exact test was used in the analysis of categorical variables, and the Mann-Whitney U test was used where parametric test assumptions were not provided in two-group mean comparisons. Univariate and multivariate logistic regression analyses were performed to determineindependent risk factors associated with the presence of fibroids, and the results are presented with odds ratio (OR) and 95% confidence intervals. The statistical significance level was accepted as 0.05.

Results

A total of 2.538 women were examined. Of these women, 437 (17.2%) had at least one fibroid, while 2102 (82.8%) had no fibroids. The demographic characteristics of the patients according to the presence of fibroids are shown in Table I. The median age of the participants was 37 (range, 18-66) years. The median BMI of all patients was 26.53 (16.80-45.79) kg/m^2.

The mean age of patients with fibroids was higher than those without (44 (24-65) vs. 34 (18-66) years; $p<0.001$). The rates of HT, DM and the presence of known fibroids, and family history of fibroids were higher in the fibroid-positive group ($p<0.001$). The rate of oral contraceptive (OC) use was higher in the group without fibroids ($p<0.001$). When previous uterine surgeries were examined, the rate of myomectomy was higher in patients with fibroids (2.5% vs. 0.2%; $p<0.001$) (Table I).

Of the 2.583 patients, 1.726 (68.0%) were asymptomatic and 812 (31.9%) were symptomatic. Fibroids were diagnosed during a transvaginal ultrasound in 437 participants with an overall prevalence of 17.2%. Fibroids were found in 12.2% (211/1726) of asymptomatic patients and 27.8% (226/812) of symptomatic patients (p<0.001). When all patients with fibroids (n=437) were considered, myomas were mostly located intramurally (61.1%), and less frequently cervically (0.5%). The characteristics of patients with fibroids according to the presence of symptoms are given in table II. Myoma diameter was significantly larger in the symptomatic group (29.5 (6-123) mm vs. 18 (7-74) mm; p<0.001). The rate of single myomas was higher in the asymptomatic group (66.4% vs.53.5%; p<0.001).

When the prevalence of fibroidsby age was examined, it was found that the prevalence reached the highest at 33% in the 41-50 years age group and decreased after 50 years of age in the entire cohort. The overall prevalence in symptomatic patients was 27.8%. It was observed that the prevalence increased with age in this group (3.4% at 18-30 years; 42.2% at 51-66 years).

The factors that independently affected the presence of fibroids are shown in table III. As a result of univariate analysis, increasing age, increasing BMI, multiparity, the presence of HT and DM, not using OCs, decreasing age at menarche, presence of known fibroids, family history of myoma, and having undergone myomectomy were associated with having fibroids.

In the multivariate model, the risk of having fibroids was 1.729 times higher in patients with a BMI of 25-29.9 kg/m^2 (95% CI: [1.053-2.840]; p<0.001). OC use (OR: 0.481, 95% CI: [0.312-0.742]; p<0.001) and increased age at menarche (OR: 0.643, 95% CI: [0.550-0.752]; p<0.001) were associated with a reducedrisk of fibroids. Multiple regression analysis showed that the risk of fibroids decreased as the parity number increased (Table III).

Table I: *Demographic characteristics of patients according to the presence of fibroids*

Variables	Fibroids No (n=2101)	Fibroids Yes (n=437)	*p*
Age (y)	34 (18-66)	44 (24-65)	**<0.001**
18-30	856 (40.7)	14 (3.2)[a]	**<0.001**
31-40	580 (27.6)	119 (27.2)	
41-50	509 (24.2)	251 (57.4)	
51-66	156 (7.4)	53 (12.1)	
BMI (kg/m^2)	26.29 (16.80-45.79)	27.63 (17.36-43.86)	**<0.001**
16-24,9	805 (38.9)	93 (21.9)[a]	**<0.001**
25-29,9	895 (43.2)	239 (56.2)	
≥30	371 (17.9)	93 (21.9)	
Number of parity			
0	547 (26.0)	41 (9.4)[a]	**<0.001**
1-3	1382 (65.8)	338 (77.3)[a]	
≥4	172 (8.2)	58 (13.3)	
Menopause	231 (11.0)	59 (13.5)	0.134
HT	57 (2.7)	35 (8.0)	**<0.001**
DM	62 (3.0)	31 (7.1)	**<0.001**
OC use	348 (16.6)	35 (8.0)	**<0.001**
Smoking	301 (14.3)	67 (15.3)	0.587
Age of menarche (y)	13 (10-17)	12 (10-16)	**<0.001**
Age at first birth (y)	22 (14-34)	21 (15-38)	0.715
Known fibroid presence	36 (1.7)	119 (27.2)	**<0.001**
Family history of fibroids	128 (6.1)	56 (12.8)	**<0.001**
Previous uterine surgery			
None	1719 (81.8)	341 (78.0)	**<0.001**
Cesarean Section	374 (17.8)	85 (19.5)	
Myomectomy	5 (0.2)	11 (2.5)[a]	
Uterine septum resection	3 (0.1)	0 (0.0)	

y: years, BMI: Body mass index HT: Hypertension, DM: Diabetes mellitus, OC: Oral contraceptive
Results are given as median (min-max) or n (% column). Mann-Whitney U test, Pearson chi-square test, and Fisher's Freeman Halton Exact test were used. [a]:Differences between groups are shown in lower case letters.

Table II. *Characteristics of patients with fibroids according to the presence of symptoms*

Variables	Asymptomatic (n=211)	Symptomatic (n=226)	*p*
Age in years	44 (27-60)	44 (24-65)	0.969
18-30	8 (3.8)	6 (2.7)	0.800
31-50	180(85.3)	190 (84.0)	
51-66	23 (10.9)	30 (13.3)	
Myoma diameter (mm)	18 (7-74)	29.5 (6-123)	**<0.001**
Number of myomas			
1	140 (66.4)	121 (53.5)[a]	**0.008**
≥ 2	71(33.6)	105 (46.4)	
Myoma location			
Intramural	146 (69.2)	121 (53.5)[a]	**<0.001**
Cervical	0 (0.0)	2 (0.9)[a]	
Submucosal	0 (0.0)	6 (2.7)	
Subserosal	65 (30.8)	97 (42.9)	

Results are given as median (min-max) or n (% column). Mann-Whitney U test, and Pearson Chi-square test were used. [a]: Differences between groups are shown in lower case letters.

Table III: *Univariate and multivariate logistic regression analysis of factors affecting the presence of fibroids*

	Univariate		Multivariate	
Variables	OR (95%CI)	*p*	OR (95% CI)	*p*
Age (y)	1.094 (1.081-1.107)	**<0.001**	1.151 (0.272-4.861)	0.848
BMI (kg/m^2)	1.071 (1.045-1.097)	**<0.001**	0.925 (0.856-1.000)	**0.049**
16-24.9	Reference	-	Reference	-
25-29.9	2.311 (1.786-2.991)	**<0.001**	1.729 (1.053-2.840)	**0.031**
≥30	2.170 (1.587-2.966)	**<0.001**	2.174 (0.903-5.233)	0.083
Number of parity				
0	Reference	-	Reference	-
1-3	3.263 (2.325-4.579)	**<0.001**	0.422 (0.264-0.672)	**<0.001**
≥4	4.499 (2.912-6.951)	**<0.001**	0.338 (0.187-0.611)	**<0.001**
Menopause	1.264 (0.930-1.717)	0.135		
HT	3.122 (2.022-4.820)	**<0.001**	1.140 (0.673-1.930)	0.627
DM	2.511 (1.611-3.915)	**<0.001**	0.931 (0.540-1.604)	0.797
OC use	0.439 (0.305-0.631)	**<0.001**	0.481 (0.312-0.742)	**<0.001**
Smoking	1.083 (0.812-1.443)	0.587		
Age of menarche (y)	0.523 (0.458-0.597)	**<0.001**	0.643 (0.550-0.752)	**<0.001**
Age at first birth (y)	1.013 (0.977-1.051)	0.474		
Known fibroid presence	21,465 (14.518-31.738)	**<0.001**	18.959 (11.816-30.422)	**<0.001**
Family history of fibroid	2.266 (1.625-3.160)	**<0.001**	1.053 (0.651-1.702)	0.834
Previous uterine surgery				
None	Reference	-		
Cesarean section	1.146 (0.881-1.490)	0.310		
Myomectomy	11.090 (3.829-32.123)	**<0.001**		
Uterine septum resection	-	-		

y: Years, BMI: Body mass index, HT: Hypertension, DM: Diabetes Mellitus OC: Oral contraceptive
Variables with p<0.05 in univariate analysis were included in multivariate analysis (Nagelkerke R Square:0.383)

Discussion

Prevalence of uterine fibroids: In this study, we evaluated the prevalence of fibroids in a representative cohort and calculated that the overall prevalence of fibroids was 17.2%. We also found that about half of women with fibroids are asymptomatic. The prevalence of fibroids was 27.8% in patients with fibroid-related symptoms and 12.2% in patients without symptoms. In our population, 25.4% of women over the age of 30 had at least one fibroid. Leiomyomas were found in almost

one out of every three gynecology patients (33%) aged 41-50 years, regardless of whether they had symptoms or not.

The prevalence of fibroids is reported in a wide range (4.5% to 68.6%) in the literature (4). The prevalence was underestimated in studies that mainly included symptomatic patients because most fibroids were asymptomatic and remained undiagnosed. On the other hand, data based on pathological evaluation of hysterectomy specimens causes overestimation (5,13,15). In addition, study population differences should also be taken into account. Marino et al. reported the rate of ultrasound-detected leiomyomas as 21.4% in their population-based cohort study, in the European population (16). In North-East Slovenia, 21.1% of randomly sampled women aged 25 to 56 years were diagnosed as having fibroids using transvaginal ultrasound (17). A study from Rize, Türkiye, reported the prevalence of fibroids, as 6.7% in gynecologic patients, which is well below the literature data (18). The absence of <1 cm fibroids in any of the patients suggests that small fibroids may have been missed. The authors suggested that geographic features might also be associated with low prevalence rates.

Although its basis is not fully explained, there are racial disparities in the prevalence of fibroids. In African American women, fibroids present more frequently, at an earlier age, in a larger size, and are more symptomatic than in Caucasian women (4). In the Nurse's Health Study, which followed 95061 premenopausal women aged 25-44 years with no previous diagnosis of fibroids for five years, the prevalence of fibroids was 37.9% in African American women, 14.5% in Hispanic women, 12.5% in Caucasian women, and 10.4% in Asian women (19). The study performed by Marsh et al. included 101 non-parous African American women and Caucasian women aged 18-30 years with no known diagnosis of fibroids or symptoms, and the prevalence of fibroids was reported as 26.5% in African American women, 6.9% in Caucasian women, with an overall prevalence of 14.9% (15).

In our study, which included only Caucasian women, we detected fibroids in 8 of 694 (1.15%) asymptomatic patients aged 18-30 years. We also found that the frequency of fibroids tended to increase with increasing age. The prevalence of myomas was highest (29%) between the ages of 41-50 years, and decreased to 16.6% in the following decade in asymptomatic patients. In a retrospective study from the United Kingdom, it was stated that women aged over 40 years were four times more likely to have fibroids than women aged under 40 years (20). Similarly, in our study, the prevalence of uterine fibroids in symptomatic patients increased gradually in menopausal ages. The increase in the prevalence of fibroids can be attributed to the fact that women in this period want to seek medical help for symptoms, which increases their hospital admissions.

Location and size of the uterine fibroids: The majority (61.1%) of myomas were intramurally located in the present study. The most common fibroid location was intramural in both asymptomatic (69%) and symptomatic (53%) patients. Two cervical and six submucosal myomas were detected in the symptomatic group, and no cervical and submucosal myomas were found in the asymptomatic group. In patients with multiple fibroids (≥3) whose leading fibroids were subserosal, other fibroids were usually located intramurally. Ahrendt et al. reported the proportion of myomas found as 46.3% intramural and 43.3% subserosal in their study (21).

Parity and myomas: In a case-control study conducted by Parazzini et al., which involved 275 patients with fibroids and 722 controls, it was reported that fibroids were less common in parous women than in nulliparous women (22). However, it is difficult to distinguish whether nulliparity is a risk factor that increases the risk of uterine fibroids or whether fertility is reduced due to the presence of uterine fibroids. Chen et al. stated that women who had given birth had a lower risk of myomas compared with nulliparous women and that the risk decreased with the increasing number of deliveries (23). In our study, we found that the presence of fibroids was inversely proportional to parity.

In the current study, the majority of patients were young (18-30 years) so they were more likely to be nulliparous. To eliminate the inconsistency, when the parity of older patients (age 41-50 years) was examined, it was found that the parity of the patients with and without fibroids was statistically similar (p=0.400). In the study performed by Marino et al., there was no significant association between parity and the presence of myomas (16). In addition to studies indicating an increased incidence of myomas in nulliparous patients (24), there are also studies reporting a decreased risk of developing uterine myomas in nulliparous women (25). Therefore, further comprehensive studies are needed to clarify the relationship between parity and the occurrence of fibroids.

Body mass index (BMI) and myomas: Many studies state that adiposity creates a relative hyper-oestrogenic state through the conversion of peripheral androgens to estrogen, which increases myoma occurrence (16,26). In univariate analysis, we found that increased BMI was associated with an increased prevalence of fibroids. In the multivariate model, the risk of myomas was 1.729 times higher in patients with a BMI of 25-29.9 kg/m^2 compared with patients with a BMI of 16-24.9 kg/m^2(95% CI: [1.053-2.840]; p<0.001). However, no linear relationship was found between the increase in BMI and the prevalence of fibroids. Wise et al. stated that there was an inverse J-shaped pattern between BMI and uterine myoma risk, very similar to the results of our study, and the peak incidence was in the 27.5-29.9kg/m^2 BMI category (27). There are also studies stating that obesity is not a risk factor (21).

Oral contraceptive use and myomas: Data from studies evaluating the relationship between OCs and fibroids are conflicting (28). Although the lack of information about the dura-

tion of contraceptive use and the age of onset in our study caused limitations in interpretation, our results showed that contraceptives had a protective role in the prevalence of fibroids.

Smoking and myomas: Studies reporting the relationship between smoking and uterine fibroids are conflicting (29). Some studies reported that smoking reduces the occurrence of uterine fibroids in a dose-dependent manner (30,31). This may be due to the anti-estrogenic effect of smoking or theincrease in tissue free radicals. Conversely, some studies found that the risk of fibroids increases with smoking (32,33). However, we could not confirm any association between fibroids and smoking. Similarly to ours, Wise et al reported no relationship between smoking and uterine fibroids (31). The opposite effects of cigarette components might explain the lack of association. For instance, it was mentioned that dioxin in a cigarette has estrogen-related effects on the uterus, which may increase cell proliferation (34).

Age at menarche and myomas: We found that patients with myomas had an earlier age at menarche (12 years vs. 13 years) and early menarche was an independent risk factor for myomas. It has been reported that the age of menarche of 16 years and above is protective against fibroid formation (35). But, Marsh et al. (15) and Bizjak et al. (17) reported no correlation between the age of menarche and the prevalence of fibroids.

Family history and myomas: Cross-sectional studies have reported an odds ratio of 2.2-4 for female relatives of women with fibroids to develop fibroids (36). In the current study, we found that a family history of fibroids (OR: 2.266; 95% CI: [1.625-3.160]; $p<0.001$) was associated with an increased risk of fibroids.

In this study, there are some limitations as well as strengths, such as the large sample size, the use of transvaginal ultrasound to define fibroids, the evaluation of symptoms, and the examination of the effects of many variables. The main limitation of our study is that the findings may not be directly generalizable to other populations because only Caucasian women were included. The lack of data on lifestyle and dietary habits could be considered other limitations.

Uterine leiomyomas remain a common health burden. Identifying women at high risk of developing fibroids could be a primary preventative measure. Measures to limit fibroid growth and fibroid-related symptoms while patients are still asymptomatic could also be considered as secondary preventatives to reduce disease burden.

Declarations

Ethics approval and consent to participate: All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of Bursa Yuksek Ihtisas Training and Research Hospital.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: FNT and NKE conducted the population study, collected, analyzed, and interpreted the data, and drafted the manuscript. All authors contributed to the writing of the paper, and have read and approved the final manuscript.

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