

# Abnormal uterine bleeding as a presenting symptom is related to multiple uterine leiomyoma: an ultrasound-based study

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**Purpose:** To determine the prevalence of uterine leiomyomas, diagnosed by ultrasound, in a private health care setting located in the central eastern region of Portugal, and to explore the demographic and clinical factors related to diagnosis and symptomatology.

**Patients and methods:** The files of 624 patients attending a private clinic in Covilhã, Portugal, from January 2 to December 31, 2010 were retrieved for evaluation. Pelvic ultrasound record, age, weight, height, age at menarche, number of pregnancies and deliveries, marital status, menstrual cycles characteristic, and contraceptive method at consultation were included in the analysis.

**Results:** Uterine leiomyoma (UL) was diagnosed by ultrasonography in 161 (25.8%) patients. A single UL was diagnosed in 80 (49.7%) patients. In 79 (49.1%) patients, the largest leiomyoma had a dimension <20 mm. Prevalence of UL was age dependent: at 11.0% for women 20–39 years old; 45.4% for those aged 40–59 years; and 19.5% for women 60 years or older. Metrorrhagia was the most distressing presenting symptom. When menorrhagia was the presenting symptom, the probability of having an ultrasound diagnosis of UL was 73.3%. Metrorrhagia or menorrhagia, as presenting symptom, was significantly related to the ultrasound diagnosis of multiple ULs.

**Conclusion:** UL was especially prevalent in women aged between 40 and 59 years. Patients with multiple ULs had significantly more abnormal uterine bleeding. In patients with menorrhagia or metrorrhagia, special attention should be taken in searching for the presence of multiple ULs during ultrasound.

**Keywords:** fibroid, leiomyoma, prevalence, ultrasound, menorrhagia, metrorrhagia

## Introduction

Leiomyomas, also known as fibroids, are the most frequent benign uterine tumors to develop during a woman's reproductive years; occurrence tends to regress after menopause.<sup>1</sup> Malign transformation of uterine leiomyoma (UL) seems to be a very rare event,<sup>2</sup> but they are symptomatic in 20%–30% of cases and are the main reason for approximately one-third of all hysterectomies in developed countries.<sup>3,4</sup> Symptoms related to UL are menstrual disorders, mainly menorrhagia, pelvic pain, and infertility, which can adversely affect pregnancy outcomes.<sup>5,6</sup> UL disproportionately affects Black women.<sup>4,7,8</sup> The etiology of UL is unknown, but it can be influenced by genetic liability,<sup>9</sup> hormonal environment,<sup>10,11</sup> and local tissue mediators.<sup>10,12</sup> Definitive prevalence of UL in the general female population is also unknown, but differs by ethnicity, age, and method used for diagnosis.<sup>13</sup> In clinical practice, transvaginal ultrasonography (TVS) is the most widespread method for evaluating UL, with an estimated accuracy of 87%–92%.<sup>14–16</sup>

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The objective of this study was to determine the prevalence of UL, diagnosed by TVS, at a private health care setting located in the central eastern part of Portugal, and to explore the demographic and clinical factors related to diagnosis and symptomatology.

## Materials and methods

The study retrospectively analyzed the medical files of all female patients who consecutively attended a gynecological consultation at a private health care setting located in Covilhã, Portugal, from December 2–31, 2010. Excluded from the study were virgins, patients who had previously undergone a hysterectomy, or those pregnant at the time of the consultation. All included patients were Caucasian, except three, who were African.

The same gynecologist (JAF), who has more than 20 years of gynecological experience and competence in the practice of gynecological ultrasound, attended all patients.

Policies of the private clinic include recording of demographic and clinical data from every patient in a standard digital database. In all cases, an office TVS was offered to the patient. The sonographic equipment used was a Nemio 17 (SSA-550A) with a PVM-651VT 6 MHz endovaginal probe (Toshiba Corporation, Tokyo, Japan).

For the anonymous use of data from patient files, written consent was obtained from the clinical director of the private health care clinic. LSB and DGT analyzed the files of 624 patients who met the inclusion criteria, and from each file they retrieved age, weight, height, age at menarche, number of pregnancies and deliveries, marital status, menstrual cycles characteristics, and contraceptive method at time of consultation. The presence, number, and largest dimension of the ULs were retrieved from TVS records. For analysis, the data recorded at the first consultation in 2010 were considered. Ultrasound records were analyzed for the presence or absence of UL, their number, location and largest dimension.

The data were organized and analyzed in Statistical Package for the Social Sciences® software ([SPSS] v 20.0 for Windows; IBM Corporation, Armonk, NY, USA), by SMN. Univariate analysis and multivariate logistic regression analysis were performed. In all cases,  $P < 0.05$  was considered significant.

## Results

Using TVS, UL was diagnosed in 161 (25.8%) of those 624 cases included in the study. From those 161 patients with an ultrasound-based diagnosis of UL, 99 (61.5%) had previous knowledge of the disease. In three patients, resectoscopic

myomectomy was proposed for treating symptomatic submucous leiomyoma.

The demographic characteristics of the studied population are shown in Table 1. The mean age was 39.6 years; 66.2% of the women were married; 68.2% reported having had at least one pregnancy and 64.2% at least one delivery; 31.6% were asymptomatic. UL was diagnosed by ultrasound in 11.0% of all women aged 20 to 39 years old, in 45.4% of all women aged 40 to 59 years, and in 19.5% of all women aged 60 years or more. Metrorrhagia and menorrhagia were the most usual presenting symptoms, and were recorded in 11.3% of all cases and in 22.3% of all women with an ultrasound diagnosis of UL.

The uterus was explored with clinical bimanual palpation and TVS. Results of clinical and ultrasound exploration of the uterus are shown in Table 2. The overall prevalence of UL was 17.0% by bimanual palpation and 25.8% by TVS. ULs larger than 3.0 cm were identified through ultrasound imaging in 24.2% of the cases.

In order to uncover significant demographic and clinical differences between women with and without ultrasound diagnosis of UL, a univariate analysis was performed (Table 3). Significant factors associated with an ultrasound-based diagnosis of UL were the following: 40 to 59 years of age; married; excessive body weight (obese); prior pregnancy or delivery; non-use of the combined pill for contraception; and symptoms of menorrhagia. However, after adjustment by multivariate logistic regression analysis, age 40 to 59 years remained the single demographic and clinical factor found to be statistically associated with ultrasonographic diagnosis of UL.

Menorrhagia, metrorrhagia, and pelvic pain were the most frequent presenting symptoms. When menorrhagia was the presenting symptom, an ultrasound imaging diagnosis of UL was made in 73.3% of cases (Table 3). Plotting a univariate analysis, metrorrhagia and menorrhagia as presenting symptoms were significantly related to the TVS diagnosis of multiple ULs, but not with the largest UL dimension (Tables 4 and 5). Although lacking statistical significance, patients diagnosed with smaller ULs seemed to be more symptomatic (Table 5).

## Discussion

The real prevalence of UL in the general population is unknown. UL prevalence has been evaluated by different methods, such as population surveys,<sup>17</sup> pathologic study of surgical specimens of hysterectomy,<sup>18</sup> postmortem of women who died without gynecological diseases,<sup>19</sup> and

**Table 1** Demographic characteristics (624 cases)

Demographic data	Total (624 cases)		Leiomyoma (161 cases)	
	n	%	n	%
Age (years)				
Range	15–77		21–71	
Median	39.62		46.65	
19 or less	12	1.9	0	0
20–39	309	49.5	34	21.1
40–59	262	42.0	119	73.9
60 or more	41	6.6	8	5.0
Education				
High school or less	394	63.1	108	67.1
College or more	230	36.9	53	32.9
Marital status				
Married	413	66.2	127	78.9
Single	155	24.8	13	8.0
Divorced	33	5.3	12	7.5
Widowed	23	3.7	9	5.6
Body mass index				
18.4 or less	20	3.2	3	1.9
18.5–24.9	371	59.5	76	47.2
25–29.9	169	27.1	56	34.8
30 or more	64	10.3	26	16.1
Age at menarch (years)				
12 or less	312	50.0	81	50.0
13 or more	312	50.0	80	50.0
Number of pregnancies				
0	198	31.7	21	13.0
1	156	25.0	54	33.5
2	163	26.1	50	31.1
3 or more	107	17.1	36	22.4
Number of deliveries				
0	223	35.7	28	17.4
1	163	26.1	60	37.3
2 or more	238	38.1	73	45.3
Miscarriage				
Total	426		140	
No	334	78.4	105	75.0
Yes	92	21.6	35	25.0
Cesarean section				
Total	401		133	
No one	321	80.0	109	81.9
One or more	80	20.0	24	18.1
Contraception				
Combined pill	207	33.2	29	18.0
Progestin pill or hormonal IUD	54	8.7	16	9.9
Other	363	58.1	116	72.1
Presenting symptom				
Screening (asymptomatic)	197	31.6	47	29.2
Metrorrhagia	67	10.7	25	15.5
Menorrhagia	15	2.4	11	6.8
Pelvic pain	61	9.8	20	12.4
Vulvar symptoms	66	9.6	13	8.1
Breast symptoms	47	7.5	12	7.5
Leukorrhea	36	5.8	6	3.7
Contraception counseling	31	5.0	5	3.1
Infertility counseling	21	3.4	0	0
Other	89	9.3	22	13.7

**Abbreviation:** IUD, intrauterine device.

**Table 2** Clinical and ultrasound uterus exploration data (624 cases)

Clinical and ultrasound data	N	%
Uterine size at gynecological examination		
Normal size	518	83.0
Uterine enlargement	106	17.0
Uterine leiomyoma at ultrasound		
Yes	161	25.8
No	463	74.2
Number of leiomyomas at ultrasound (161 women)		
Single	80	49.7
Multiple	81	50.3
Dimension of largest leiomyoma at ultrasound (161 women)		
<20 mm	79	49.1
20–29 mm	43	26.7
30–39 mm	18	11.2
40–49 mm	11	6.8
>50 mm	10	6.2
Previous patient knowledge about leiomyoma (161 women)		
Yes	99	61.5
No	62	38.5

pelvic ultrasonography,<sup>13,20,21</sup> with, as expected, different results.

Kratochwil et al<sup>22</sup> introduced ultrasound imaging of feminine pelvic organs in 1972. In 1980, Muram et al<sup>23</sup> defined criteria for UL identification with TVS as a relatively spherical mass that is echogenically different from the surrounding myometrium. Since then, TVS has become the most noninvasive, lowest-cost, and widespread method for evaluation of uterine pathology, with highly accurate performance.<sup>14–16</sup> The main disadvantage of ultrasound is that it is an operator- and device-dependent technique.<sup>24</sup> In order to improve UL diagnosis accuracy, saline contrast sonohysterography and three-dimensional ultrasound have been proposed, although with conflicting results.<sup>24,25</sup> Nowadays, two-dimensional pelvic ultrasonography remains the best method for routine detection of ULs.<sup>24,25</sup> Ultrasonography has been shown to be an insufficient method of myoma mapping, and magnetic resonance imaging should be preferred for surgical therapy planning.<sup>25</sup>

In the present study, we found a 25.8% overall prevalence of UL, with the highest prevalence (45.4%) in women aged 39–50 years, which is in accordance with previous ultrasound-based studies.<sup>13,20,26</sup> Multiple ULs were present in 50.1% of cases, which is lower than that reported in surgical specimens by Cramer and Patel (84%).<sup>18</sup> In contrast to Cramer and Patel's findings, only 49.1% patients had a UL larger than 20 mm. A previous diagnosis of UL had been made in 99 (61.5%) patients, who were in watchful waiting

**Table 3** Univariate analysis of demographic and clinical characteristics between patients with and without sonographic diagnosis of uterine leiomyoma

Demographic and clinical data	Uterine leiomyoma at ultrasound		P-value
	No	Yes	
Age (years)			
19 or less	100.0%	0.0%	0.0001
20–39	89.0%	11.0%	
40–59	54.6%	45.4%	
60 or more	80.5%	19.5%	
Education			
High school or less	72.6%	27.4%	0.134
College or more	77.0%	23.0%	
Marital status			
Married	69.2%	30.8%	<0.0001
Other	83.9%	16.1%	
Body mass index			
18.4 or less	85.7%	14.3%	0.002
18.5–24.9	79.2%	20.8%	
25–29.9	66.9%	33.1%	
30–34.9	62.3%	37.7%	
35 or more	54.5%	45.5%	
Age at menarch (years)			
12 or less	74.0%	26.0%	0.500
13 or more	74.4%	25.6%	
Pregnancy			
No	89.4%	10.6%	<0.0001
Yes	67.1%	32.9%	
Number of pregnancies			
1	65.4%	34.6%	0.741
2	69.3%	30.7%	
3 or more	66.4%	33.6%	
Delivery			
No	87.4%	12.6%	<0.0001
Yes	66.8%	33.2%	
Number of deliveries			
1	63.2%	36.8%	0.120
2 or more	69.3%	30.7%	
Miscarriage			
No	68.6%	33.7%	0.143
Yes	62.0%	38.0%	
Cesarean section (401 women)			
No one	66.3%	33.7%	0.360
One or more	69.2%	30.8%	
Contraception			
Combined pill	85.9%	14.1%	<0.0001
Progestin pill or hormonal IUD	70.4%	29.6%	
Other	69.6%	30.4%	
Menopause			
No	76.1%	23.9%	0.011
Yes	64.4%	35.6%	
Presenting symptom			
Menorrhagia	26.7%	73.3%	<0.0001
Metrorrhagia	63.2%	36.8%	
Pelvic pain	64.3%	35.7%	
Other	78.8%	21.2%	

**Abbreviation:** IUD, intrauterine device.

**Table 4** Presenting symptoms according to number of uterine leiomyomas at ultrasound

Presenting symptom	Uterine leiomyomas at ultrasound		P-value
	Multiple	Single	
Metrorrhagia	72.0%	28.0%	0.018
Menorrhagia	72.7%	27.3%	
Pelvic pain	55.0%	45.0%	
Other	41.9%	58.1%	

management, which has been considered as a safe management option for asymptomatic UL.<sup>27,28</sup> Except in three cases submitted to resectoscopy for treatment of symptomatic submucous myomas, the main component of the leiomyomas was intramural. A purely intramural myoma represents a temporary status, and its growth is dependent on the existing hormonal conditions of the woman.<sup>29</sup>

Most of the knowledge about demographic and clinical risk factors for UL is based on results of large populations survey studies. Risk factors such as age, ethnicity, education, hormonal factors, diet, physical exercise, oral contraceptives use, childbirth, smoking and tissue injury has been reported, with conflicting results. In accordance with other ultrasound-based studies,<sup>13,20,26</sup> after multivariate statistical analysis, we don't found any demographic or clinical risk factor for UL, with exception of age.

The most common symptom of UL is abnormal uterine bleeding, especially menorrhagia.<sup>5</sup> The mechanism of leiomyoma-associated menorrhagia is unknown, but submucous localization, vascular defects, and impaired endometrial hemostasis have been suggested as possible explanations.<sup>30,31</sup> Even small ULs without distortion of the endometrial cavity can alter myometrial vascularization and contractibility. A meta-analysis conducted by Benecke et al<sup>32</sup> reported that intramural ULs may have a negative impact on fertility. In our series, menorrhagia was significantly associated with multiplicity of ULs, but not with the volume of the largest one, suggesting the importance of factors other than those associated with distortion of the myometrium and endometrial cavity. Extracellular matrix that embed UL cells influence both

**Table 5** Presenting symptoms according to size of largest uterine leiomyoma at ultrasound

Presenting symptom	Size of largest uterine leiomyoma		P-value
	<3 cm	≥3 cm	
Metrorrhagia	60.0%	40.0%	0.215
Menorrhagia	72.7%	27.3%	
Pelvic pain	75.0%	25.0%	
Other	80.0%	20.0%	



normal myometrial and UL cells, promoting proliferative activity and decreasing apoptosis.<sup>33,34</sup> Previous ultrasound-based studies<sup>20–35</sup> have reported that the presence, number, and volume of leiomyomas are unrelated to abnormalities in the menstrual cycle. Other studies,<sup>36,37</sup> but not all,<sup>38</sup> suggest that menstrual symptoms are related to tissue layer location in the uterine wall and with the axial position of leiomyomas. In our study, multiplicity of ULs was significantly related to abnormal uterine bleeding (menorrhagia and metrorrhagia) as a presenting symptom.

Currently, most women with menstrual disorders and multiple ULs are scheduled for medical therapy followed by hysterectomy or myomectomy.<sup>39</sup> Hysterectomy seems a good option when childbearing wishes have been fulfilled;<sup>39</sup> but it is not devoid of risks, morbidity and mortality as for any surgical procedure. Myomectomy is indicated for those women who wish to retain their fertility.<sup>39</sup> The major disadvantage of surgical myomectomy is leiomyoma recurrence. In next 5 years, more than one-third of that women submitted to myomectomy will need additional surgical intervention for treatment of newly developed ULs.<sup>40</sup> Minimally invasive procedures, such as laparoscopic myolysis, uterine artery embolization, uterine fibroid embolization, and magnetic resonance-guided focused ultrasound, as standard practice for treatment of symptomatic multiple ULs are currently limited.<sup>41</sup> It seems obvious that new treatments better than surgical approaches are needed for the management of symptomatic UL.

In recent years, intense scientific research has brought new insights on UL biology. The development of ULs has been shown to be dependent of sex steroids, especially progesterone,<sup>42,43</sup> and many leiomyoma-related growth factors have been identified, including epidermal growth factor, platelet-derived growth factor, transforming growth factor beta, insulin-like growth factor, activin, and myostatin. We speculate that, in patients with multiple ULs and menstrual disorders, each UL can produce different kinds of growth factors or other biological mediators that may have additive negative effects on the myometrial and endometrial environment.

Discovery of selective progesterone receptor modulators (SPRMs) has provided a new paradigm for treatment of symptomatic UL. Antiproliferative, growth factors down-regulation, and proapoptotic actions of SPRMs had been reported in vitro studies over cultured leiomyoma cells.<sup>43</sup> Randomized, placebo-controlled clinical trials have demonstrated that the SPRM ulipristal can suppress menstrual bleeding, restore normal levels of hemoglobin, reduce UL volume, and improve leiomyoma-related symptoms.<sup>44,45</sup>

The main objective of symptomatic UL treatment is to regress symptomatology, because expectant management is suitable for most asymptomatic leiomyomas.<sup>27,28</sup> It is expected that new therapies for the treatment of UL-associated symptomatology will be developed, based on the growing knowledge of functional aspects and regulatory mechanisms of leiomyoma biology and uterine homeostasis.

## Conclusion

To our knowledge, this is the first population study conducted in Portugal to assess the prevalence and demographic and clinical factors associated with the diagnosis of UL by ultrasound. In our Portuguese population, the prevalence of uterine leiomyoma increases with age, and was similar to that reported in literature for White women.

Menorrhagia and metrorrhagia were the more distressing symptoms, especially in patients with multiple ULs diagnosed by TVS. In patients with abnormal uterine bleeding, special attention should be taken to search for multiple leiomyomas during pelvic ultrasound examination.

Further studies are needed to assess the biology and symptomatic impact of multiple versus single ULs, in order to find more efficient therapeutic approaches.

## Disclosure

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