Full length article

Epidemiology of uterine myomas and clinical practice in Spain: An observational study

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A R T I C L E   I N F O

A B S T R A C T

Objective: Characterization of the clinical features of symptomatic uterine myomas in Spanish women visiting the gynaecologist, including impact on quality of life and possible risk factors, description of main therapeutic approaches, and evaluation of symptom and quality of life progression 6 months after inclusion in the study.

Study design: This was an observational, epidemiological, non-interventional, multicentre study performed between June 2015 and March 2016. Data were collected at baseline and follow-up visits 6 months apart from women with a diagnosis of uterine myomas and visiting a participating gynaecologist in outpatient units of private clinics or public hospitals in Spain. Data consisted of a gynaecological clinical inspection, an interview with open questions to the patients, and self-administered generic questionnaires. The main outcome measures were socio-demographic data, clinical history, myoma clinical features, symptomatology, data on surgical choices, patient satisfaction, and risk factors associated to myomas.

Results: Data were collected from 569 patients (1,022 myomas) at 56 hospitals and private gynaecological offices in Spain. Most patients (85%) presented between 1 and 3 myomas, predominantly intramural and subserosal. Most common symptoms reported heavy menstrual bleeding and pelvic pain, and the mean ($\pm$SD) symptom severity score in the UFS-QoL questionnaire (range 0–100) was 50.89 ± 20.85. Up to 60.5% of patients had an indication of surgery (55.8% myomectomies, 40.4% hysterectomies) to treat their uterine myomas and 39.5% followed other therapies, mainly pharmacological. After six months of treatment, all patients had experienced significant reduction in symptoms and improvement of quality of life.

Conclusions: The most frequent symptoms reported by women diagnosed with uterine myomas were heavy menstrual bleeding, pelvic or abdominal pain and dysmenorrhea; QoL was impaired reflecting high symptom distress. We found that surgery was the main therapeutic approach to manage uterine myomas in Spain. Both surgical and non-surgical treatments achieve relevant improvements in symptom severity and quality of life.

Introduction

Uterine myomas represent 20% of all benign tumours in women of childbearing age and, according to some estimates, they can affect up to 70–80% of women [1–3]. In addition to this high prevalence, it is estimated that 25–40% of myomas generate symptoms that ultimately impact on the quality of life and the daily activities of the affected women, or become so severe as to require specific treatment [3–5]. Myomas can cause heavy menstrual bleeding, anaemia [6], bowel and bladder dysfunction,

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urinary incontinence, infertility and recurrent miscarriage [7]. Risk factors include genetics, ethnicity, age, early menarche, caffeine and alcohol intake, and obesity [3,8,9].

The incidence rates and prevalence of uterine myomas are likely underestimated as they only take into account those women who have symptoms or consult a healthcare professional [1,3]. The choice of treatment requires knowledge of the clinical features (myoma size, localization and number) for optimal outcomes, and also of the patient's symptomatology and preferences (i.e. desire to preserve fertility or avoid 'radical' surgery) [8,10]. Although hysterectomy was long considered the only therapeutic option for the treatment of severe myomatosis, other techniques are currently available now which allow for a more individualized approach and preservation of the uterus [8].

Multiple studies have highlighted the importance of symptoms in the quality of life of the patient [7,11,12]. In spite of this, in many cases the time between the onset of symptoms and the beginning of a medical treatment can be long. Indeed, a study of myomatosis in five large European countries revealed that between 9.0% and 32.5% of women waited ≥5 years before seeking treatment [13]. Spain had the highest proportion of diagnosed but untreated myomas (57.4%) [13].

The primary aim of this observational epidemiological study (EME Study: Spanish for 'Epidemiological Study on Uterine Myomas in Spain') was to describe the clinical features of uterine myomas and their progress in diagnosed women in Spain. Secondarily, we evaluated the quality of life of women suffering from this condition and possible risk factors. We also described the different therapeutic approaches and evaluated symptom progression and quality of life 6 months after inclusion in the study.

Methods

This is a non-interventional, epidemiological, multicentre study performed between June 2015 and March 2016 in Spain. The primary objective was the clinical characterization of symptomatic myomas in women visiting a gynaecologist in Spain. Other objectives included the assessment of the impact of the symptoms on patient's quality of life; the average time between programming and surgical intervention of the myomas; estimation of the fraction and characteristics of myomas subjected to surgery; the determination of the frequency of different risk factors typically associated with presence of uterine myomas; and, finally, the assessment of the level of acceptance of the patient regarding the need for surgery. The protocol and all study materials were approved by the Clinical Research Ethics Committee of Teknon Medical Center - Quirón Hospital Group on June 2, 2015. The EME study reference number is GR-OB-02-2015.

Participation in the study did not imply any risk for the patients nor did it involve the modification of usual therapeutic guidelines. It did not require the prescription of any particular drug. The study was carried out in accordance with the principles adopted by the 18th World Medical Assembly (Helsinki, 1964).

Study population and procedure

A total of 57 gynaecologists working at gynaecologic units at public hospitals (80.0%) and private consultation offices (20.0%) accepted to participate. Each gynaecologist collected data for 10 patients. The gynaecologists had a mean 26.6 ± 8.3 years of experience in clinical practice and the participating centres attended between 30 and 1,400 patients weekly.

To be included in the study patients had to be older than 18 years with a confirmed diagnosis of single or multiple uterine symptomatic myomas. In addition, they had to agree to participate in the study and provide their informed consent. Pregnant women were excluded from the study.

Data were collected in consultations according to usual clinical practice in two sequential visits: the baseline visit and the follow-up visit. In the baseline visit, the patient was informed of the study and signed the informed consent. The gynaecologist completed all sections of the data collection notebook, which included gynaecological and obstetric history of the patient and assessment of the current episode: characteristics of the myomas (according to ultrasound (US)), current symptoms and previous treatments. Consecutively the patient filled a form in which specific symptoms and an assessment of general health status, habits and quality of life was recorded. In addition, the therapeutic approach was also recorded by the gynaecologist, confirming (or not) the need of surgical intervention, as well as the selected procedure and the estimated date of surgery.

At the follow-up visit (6 months ±2 weeks after the baseline visit) the gynaecologist recorded data on the overall patient's progress, as well as the treatment followed and whether or not surgery had been carried out; characteristics of the myomas in patients not undergoing surgery were re-assessed. The patient again provided data on the associated symptomatology, general health status and quality of life.

Measurement instruments

Socio-demographic data, medical record, risk factors and other variables were obtained by the gynaecologist based on the clinical interview and examination, and using both from generic questionnaires and open questions to the patients. Transvaginal sonography (TVS) provided information on the number of myomas and their location, as well as their relation to the myometrium (submucosal, intramural, subserosal) using the classification system proposed by the Working Group on Menstrual Disorders of the International Federation of Gynaecology and Obstetrics (FIGO) [14]. The symptom intensity was assessed by the patient with a Visual Analogue Scale (VAS) with a score of 0–10 where a higher value denotes greater severity. Health-related quality of life was assessed with the Spanish version of the EuroQoL-5D [15], (ranging from 0–having concerns- to 1–no concerns) and the Uterine Fibroids Symptom and Health-related Quality of Life Questionnaire (UFS-QoL) [7], in which scores for symptom severity range from 0 to 100, with higher scores indicating increased severity. Total scores for health-related quality of life range from 0 to 100, with higher scores indicating a better quality of life.

Statistical analysis

Categorical variables were presented as lists of frequencies and proportions. Quantitative variables were described as means and standard deviations or as medians with maximum and minimal values. All tables, figures or graphs were calculated from the number of valid cases (N). Categorical variables were analysed by Pearson's Chi-Square Tests and the effect size was measured by Odds Ratio). In case of continuous variables, analysis was carried out by One-way ANOVA and effect size measured by Cohen's d. In case of non-normally distributed or ordinal data, U-Mann Whitney test were performed. Multivariate methods were used in order to study the independence of the factors detected. Paired tests (McNemar and Wilcoxon test) were used to assess the evolution of quality of life, patient symptomatology, and tumour volume. Statistical analysis was performed using SPSS 22.0 statistical software for Windows.

Results

In this observational study we collected data on 569 women diagnosed with uterine myomas. The sociodemographic

Table 1
Patient demographic and gynaecological data (n = 569).

Age (years), mean ± SD	42.99 ± 6.36
Weight (kg), mean ± SD	66.27 ± 11.41
Height (cm), mean ± SD	163.41 ± 6.14
BMI, n (%)	
<25	348 (61.16%)
25–30	156 (27.42%)
>30	58 (10.19%)
Ethnic origin, n (%)	
Caucasian	489 (86.1)
Latin-American	64 (11.3)
African	11 (1.9)
Asian	2 (0.4)
Other	2 (0.4)
Menarche (age), mean ± SD	12.29 ± 1.40
Gynaecological check-ups, n (%)	
Every year	362 (64.0)
Every two years	61 (10.8)
Irregularly	119 (21.0)
Never	24 (4.2)
NA	3 (0.5)
Current gynaecological status, n (%)	
Childbearing age	362 (64.2%)
Perimenopausal	199 (35.3%)
Postmenopausal	3 (0.5%)
Parity, mean ± SD	
Term deliveries	1.20 ± 1.12
Pre-term deliveries	0.06 ± 0.34
Abortions	0.31 ± 0.64

Table 2
Uterine myomas characterization according to TVS study, n (%).

No. of myomas per patient (n = 569)	
1	289 (50.8)
2	117 (20.6)
3	79 (13.9)
4	32 (5.6)
5	15 (2.6)
>5	37 (6.5)
No. of myomas studied per patient (n = 1,022)	
1	582 (56.95)
2	278 (27.20)
3	162 (15.85)
Type of myoma[a] (n = 1022)	
Submucosal	239 (23.4)
Intracavitary pedunculated (Type 0)	35 (3.4)
<50% intramural (Type 1)	86 (8.4)
≥50% intramural (Type 2)	118 (11.5)
Intramural	347 (34.0)
Endometrial contact (Type 3)	105 (10.3)
Intramural (Type 4)	242 (23.7)
Subserosal	363 (35.5)
≥50% intramural (Type 5)	183 (17.9)
<50% intramural (Type 6)	161 (15.8)
Pedunculated (Type 7)	19 (1.9)
Other	65 (6.4)
Submucosal and subserosal (Type 2–5)	63 (6.2)
Other (Type 8)	2 (0.2)
NA	8 (0.8)
Localization of the myomas (n = 1,018)	
Posterior	194 (19.06)
Anterior	348 (34.18)
Fundus	319 (31.34)
Lateral left	87 (8.55)
Lateral right	70 (6.88)

TVS = Transvaginal sonography/Ultrasound NA = Not available.
[a] According to FIGO classification [14], as specified by the numbers.

Table 3
Symptomatology and QoL at baseline (n = 564).

Previous myoma symptoms, n (%)	
Yes	276 (48.9)
No	288 (51.1)
Current Symptoms, n (%)	
Heavy menstrual bleeding	493 (86.6)
Pelvic pain	279 (49.0)
Dysmenorrhoea	258 (45.3)
Urinary dysfunction	100 (17.6)
Dyspareunia	83 (14.6)
Dyschezia/constipation	54 (9.5)
Infertility	38 (6.7)
Other	24 (4.2)
UFS-QoL[a], mean ± SD:	
Global	58.20 ± 22.28
Concern	46.29 ± 28.49
Activities	57.81 ± 25.02
Energy/mood	58.69 ± 25.34
Control	59.54 ± 25.10
Self-conscious	71.84 ± 30.18
Sexual function	59.39 ± 26.65

UFS–QoL = Uterine Fibroid Symptom and Quality of Life questionnaire.
[a] Ranging from 0 (worse QoL) to 100 (better QoL). Values ≥86 reflects QoL compatible with healthy women, while ≤62 indicated bad QoL related to UF [8].

characteristics and basic gynaecological background of this population can be found in Table 1. Most patients (64.0%) reported having yearly gynaecological check-ups, and 24.4% of the patients expressed a wish to have children in the future. Almost all women in the study (95%) had no previous ovarian, uterine (other than uterine myomas) or mammary pathologies, and more than a quarter of the patients (25.8%) reported relatives with uterine myomas, from whom the most (71.5%, n = 103) was the mother. Almost half (48.9%) of the women surveyed experienced previous episodes of symptoms associated to uterine myomas.

Most patients (85%) presented between 1 and 3 myomas, predominantly intramural and subserosal (Table 2). The mean (±SD) total volume of the 3 largest myomas found per patient was of 201.34 (±965.26) cm^3, with subserosal myomas being the largest.

The most common symptoms reported were heavy menstrual bleeding (up to 86% of the patients), pelvic pain and dysmenorrhoea (around half of the patients) (Table 3). Patients in the study had a mean in the generic quality of life questionnaire EuroQoL 5-D (ranging from 0 –having concerns- to 1 –no concerns) of 0.75 (range 0.08–1). In the UFS-QoL questionnaire (ranging from 0 to 100, with higher scores indicating increased severity), the mean (±SD) symptom severity score was 50.89 (±20.85), which reflects high symptom distress [7]. The total and subscale QoL scores are shown in Table 3. Symptoms were also analysed according the myoma location (i.e. submucosal, intramural, subserosal). Women with submucosal myomas reported significantly higher rates of heavy menstrual bleeding (OR 2.97, p = 0.0001) as well as significantly lesser rates of pelvic pain (OR 0.51 p < 0.0001) and urinary dysfunction and/or dyschezia (OR 0.52, p = 0.0021).

Following the baseline visit, 344 (60.5%) patients had an indication of surgery and 225 (39.5%) patients had an indication to follow other treatments (no data were recorded for pharmacological or other non-surgical treatments). The surgical procedure was

actually performed in 234 (68% of the initially scheduled) of the patients within six months of the baseline visit, which represents a 41.1% of the total patients at the inclusion visit. The average time (±SD) from programming and actual surgical procedure was of 99.58 (±55.16) days. Table 4 shows the surgical procedures chosen

Table 4
Surgical procedures indicated and performed, n (%).

	Indicated at Baseline (n = 344)	Performed at Follow-up (n = 234)	Performed vs Indicated (%)
Laparotomic myomectomy	60 (17.4)	40 (17.1)	66.6
Laparoscopic myomectomy	26 (7.6)	11 (4.7)	42.3
Hysteroscopic myomectomy	106 (30.8)	90 (38.5)	84.9
Hysterectomy	139 (40.4)	85 (36.3)	61.2
Other surgical options[a]	8 (2.3)	8 (3.4)	100
NA	5 (1.5)	–	–

NA = not available.
[a] Data not specified.

Table 5
Number of myomas removed by type of surgery and type of myoma[a], n (%).

	Myomectomy			Hysterectomy	Other[b]	Total
	Laparotomy	Laparoscopy	Hysteroscopy			
Submucosal	4 (9.5)	0 (0)	21 (50.0)	6 (14.3)	11 (26.2)	42 (100)
Intramural	6 (10.7)	2 (3.6)	10 (17.9)	14 (25.0)	24 (42.9)	56 (100)
Subserosal	15 (22.4)	2 (3.0)	6 (9.0)	26 (38.8)	18 (26.9)	67 (100)
Other	6 (23.1)	3 (11.5)	2 (7.7)	11 (42.3)	4 (15.4)	26 (100)

[a] Type of myoma is based on the biggest myoma per patient. Some patients could have undergone a technical procedure on the basis of the symptoms associated to a fibroid different than the biggest.
[b] Not specified.

by the gynaecologists in this study. Half of the procedures performed were myomectomies (laparotomy, laparoscopy, or hysteroscopy). Table 5 shows the technical approach used related to the type of myoma, with hysteroscopic myomectomy mainly used for removal of submucosal myomas, whereas intramural or subserosal myomas were treated mostly by hysterectomy and the conservative approaches (laparoscopy or laparotomy myomectomy) were used less frequently. Fig. 1 summarizes the patient flow according to chosen surgical procedures. We found that the surgical procedure was well accepted by 74.2% of the patients, while 25.8% of them expressed a negative concern.

Symptom severity (UFS-QoL subscale) improved from 54.47 ($\pm$20.40) to 16.66 ($\pm$19.54) for patients who underwent surgery between baseline and follow-up visit; patients which did not have surgery (other treatments) improved from 48.71 ($\pm$20.91) to 27.51 ($\pm$22.28) as well ($p < 0.001$ for both cases) (Fig. 2). A sub-analysis in hysterectomized and non-hysterectomized patients showed a better quality of life in the first group (total UFS-QoL 69.99 vs 87.0, respectively; $p = 0.0001$). This was observed both for the global score and all the QoL domains. Additionally, Fig. 3 shows the percentages of patients reporting symptoms according to therapeutic approach (surgical or non-surgical) at the baseline and follow-up visits. As expected, patients undergoing surgery experienced a significant reduction in specific symptoms. However, those under other treatments, although to a lesser degree, also experienced a significant reduction in symptoms ($p < 0.001$ for all symptom's reductions in both groups).

Total myoma volume was significantly higher than the median in women with BMI $\geq$ 30 (OR = 2.2, 95%CI 1.15–4.23) and nulliparous (OR = 2.00, 95%CI, 1.24–3.23). However, we did not find an association of myoma volume with age, habits (smoking, alcohol), ovarian pathology, age of menarche, other non-gynaecologic benign cancers, dyslipidaemia, parity, or familial antecedents of uterine myomas. Patients who initially were selected for a surgical procedure were those with higher estimated total myoma volume, 310.48 ($\pm$1465.83) cm^3. For those patients following non-surgical treatments, a significant decrease in estimated myoma volume was observed between baseline and follow-up visits, from 120.65 ($\pm$143.45) cm^3 to 96.41 ($\pm$139.63) cm^3 ($p < 0.001$, Wilcoxon test).

An association was observed between the volume of the myomas and the severity of specific symptoms, and this was observed in two ways. Firstly, a higher percentage of patients reported symptoms such as pelvic pain, dyschezia/urinary dysfunction and constipation, which were significantly associated with larger myomas (OR = 2.81, 2.56 and 2.84, respectively, [$p < 0.001$ in all cases]). Conversely, smaller myomas were significantly associated with a higher percentage of patients reporting bleeding (OR = 0.51, $p = 0.0093$) and dysmenorrhea (OR = 0.69, $p = 0.0284$). Additionally, a lower total symptom severity score was significantly associated with smaller myomas, with Cohen's d = 0.37 ($p < 0.0001$) for scores obtained from the VAS, and Cohen's d = 0.22 ($p = 0.0079$) for UFS-QoL scale symptom severity score. Finally, a higher total EQ-5D-3 L score was significantly associated with smaller myomas (Cohen's d = 0.20, $p = 0.0164$).

Comment

Our study shows that the profile of Spanish women presenting symptomatic uterine myomas is: childbearing age, with previous episodes of myomatosis, presenting 1–3 myomas in the majority of the cases, predominantly intramural and subserosal. The most frequent symptoms reported were heavy menstrual bleeding, pelvic or abdominal pain and dysmenorrhea. Symptom intensity decreased significantly with the intervention in both the operated and non-operated populations. Patients' Quality of Life significantly improved between the diagnosis/inclusion and the follow-up visit 6 months later, both in operated and non-operated patients. A surgical treatment was indicated for most patients, usually taking place within 3 months. Myomectomy, in its different variants, was the more frequently practiced surgery, followed by hysterectomy.

A 2007 epidemiological study of uterine myomas in 5 large European countries estimated the prevalence in Spain at 18.8% on women aged over 18, with an additional 19.1% suffering from undiagnosed bleeding symptoms [13]. Up to 28% of the women had suffered the symptoms for > 1 year without seeking assistance and Spain had the highest proportion (57.4%) of women with a
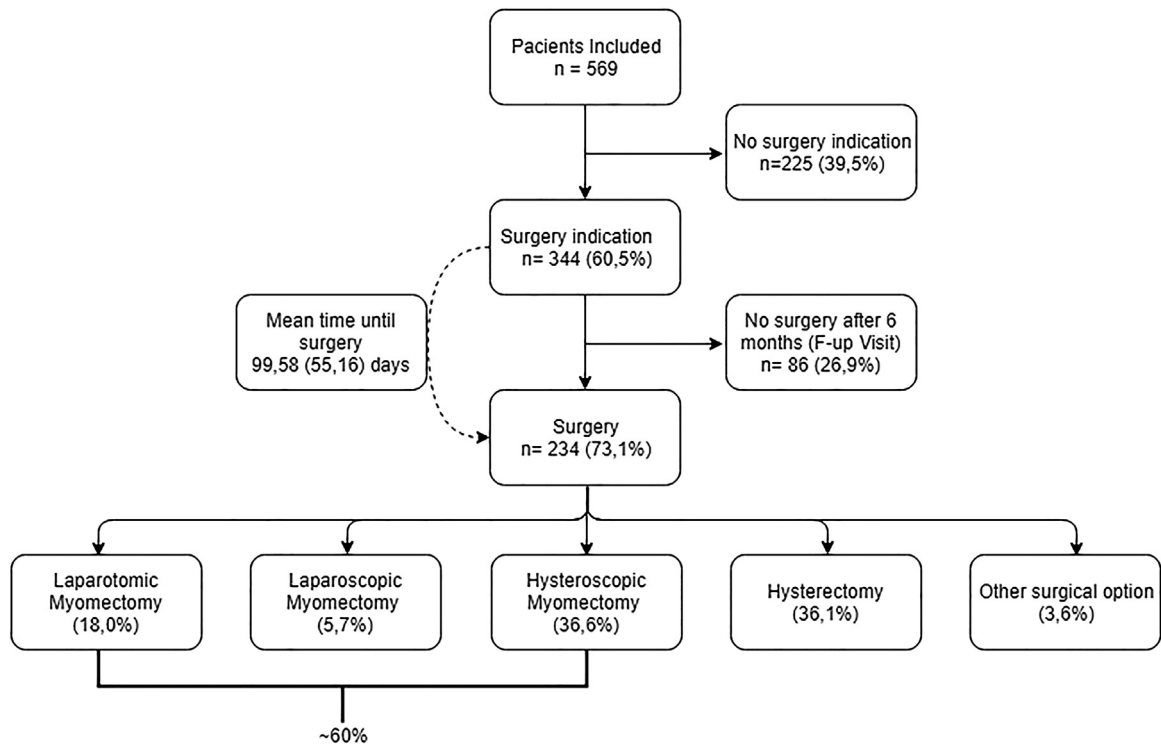
Fig. 1. Patient flow according to therapeutic approach and surgical procedure.
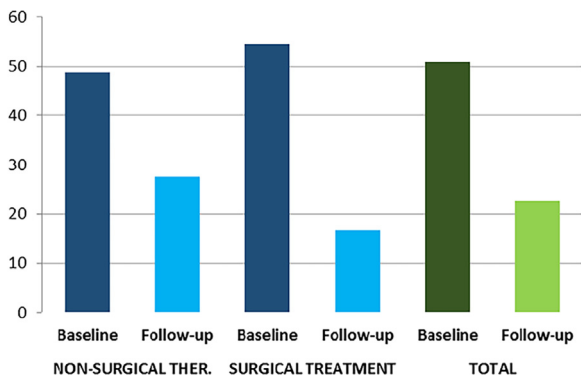

Fig. 2. Progression of mean UFS-QoL symptom severity score from the baseline to the follow-up visit.

diagnosis of myomas who were untreated. Our study reveals that about half of the patients interviewed had presented myoma symptoms previously and that, although up to 64% of women visited the gynaecologist regularly, a large proportion (25%) had done so irregularly (<2 years) or never. The delay in seeking treatment could reflect limited access to medical facilities, reluctance to treatments perceived as invasive, or tolerance to the symptoms.

A positive correlation was found between myoma volume and BMI ≥ 30 or nulliparity. Obesity has often been positively associated to uterine myomas, due in part to increased levels of free circulating estrogens in these women [16]. Similarly, past studies have shown that an increasing number of term pregnancies decreases myoma risk [17]. Nulliparity has been generally associated with an increased risk for reproductive pathologies, including breast, ovarian and uterine cancers. It has been suggested that this risk is related to the increased number of
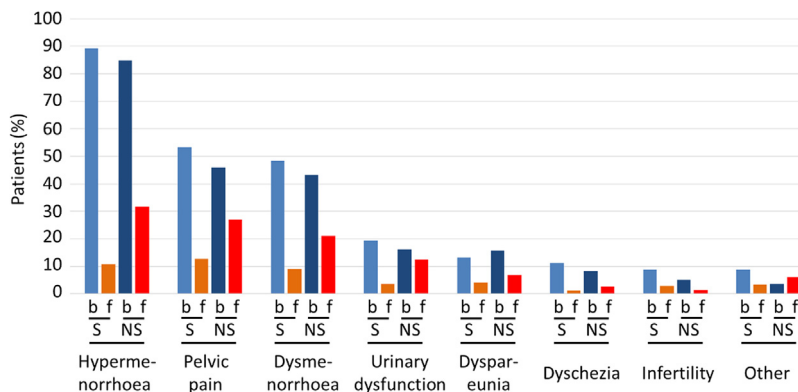
Fig. 3. Progress of symptomatology between the basal (b) and follow-up (f) visits for patients treated surgically (S) or non-surgically (NS). Symptom categories are not mutually exclusive.

ovulatory cycles, and so might be preventable by utilization of contraceptives [18].

The statistically significant association observed between myoma volume and symptom severity confirms previous studies; that is, the clinical relevance of myoma size [19,20]. Statistically significant association between the larger myomas and quality of life provide evidence that shrinking myomas, and not only controlling bleeding, should be taken into account when considering type of treatment. Interestingly, a statistically significant inverse association was observed between myomas size and bleeding and dysmenorrhea, showing that heavy bleeding (and pain associated) is not necessarily related to larger myomas. Indeed, as shown in the location sub-analysis, higher rates of heavy bleeding were observed for submucosal myomas, which, in turn, are the smallest.

Although until recently hysterectomy was the preferred treatment of uterine myomas [21], currently alternative approaches are possible [8]. Indeed, a trend for a decrease of hysterectomies in favour or less invasive surgical or non-surgical techniques such us myomectomy, endometrial ablation or uterine artery embolization has been reported [22]. We found in our study that hysteroscopic or laparoscopic myomectomy and hysterectomy are used almost as often, which might reflect a preference for minimally invasive techniques or an interest by the patient in preserving fertility, as mentioned above. The population not undergoing surgery (which may include pharmacological treatment or other non-surgical techniques) also presented a significant clinical improvement and, remarkably, in many cases to a degree not far from those undergoing surgery. We think this is something to take into account when selecting a treatment approach, especially for those patients for whom surgery is not an option (e.g. coagulation disorders) or should be considered with caution (e.g. fertility preservation). Further research, now ongoing, will address the various options taken by the clinicians to treat these patients and the outcomes observed, including pharmacological therapies such as ulipristal acetate, GnRH analogues, oral contraceptives or tranexamic acid, or the use of a levonorgestrel IUD.

To our knowledge, this is the first large-scale epidemiological study on uterine myomas performed specifically in the Spanish population. Additionally, and compared to previous studies [13], our work presents physician-validated clinical data, a description of myoma management in real clinical practice, and a six months follow-up. However, as it is the case in other observational studies, a limitation of our analysis is that the results could be biased towards the symptomatology and management of myomas in women who visit the gynaecologist regularly and are willing to follow a treatment, who could not be representative of the general population. Further, our study did not collect data on the non-surgical treatments (39% of the patients).

Conclusion

In Spanish women diagnosed with uterine myomas, the most frequent symptoms reported were heavy menstrual bleeding, pelvic or abdominal pain and dysmenorrhea; QoL was impared reflecting high symptom distress. Surgery was the main therapeutic approach, although up to 40% of patients were treated only with other non-surgical therapies. We find significant improvements in quality of life and symptomatology 6 months after diagnosis in patients undergoing surgery as well as in those receiving other currently available medical therapies. A combination of myoma clinical impact and characteristics (including size and location), as well as personal choices by the patient should guide any individualized treatment approach.

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