UNIVERSIDADE DA BEIRA INTERIOR
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Epidemiological factors associated with Uterine Fibroids

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To my sister and brother, although we are apart I want you to know that you are always on my mind and that I miss being with you both.

Finally, I would like to thank my parents who have been a constant support and inspiration at all times. Their love and encouragement gave me the strength I needed to accomplish my goals.

Resumo

Introdução: Os miomas uterinos são a neoplasia benigna mais comum no trato genital feminina. No entanto, a prevalência desta patologia na população em geral não é conhecida, o que justifica esta investigação.

Objetivo: Avaliar quais os fatores epidemiológicos associados com os miomas uterinos.

Methodologia: Estudo transversal com uma componente descritiva e analítica.

Para todas as pacientes foi preenchido por rotina um ficheiro informático e foi-lhes realizada uma ecografia pélvica transvaginal ou transretal. Foi registada a idade das pacientes no momento da consulta, peso, altura, idade da menarca, número de gravidezes e de partos, estado civil, nível de escolaridade, ciclo menstrual e método contracetivo utilizado.

Através da análise por ecografia foi registada a presença de miomas uterinos, o número e a maior dimensão do maior mioma.

Resultados: Da totalidade das mulheres (n = 624) estudadas pela ecografia pélvica, 161 (25,8%) apresentaram miomas uterinos. Em 49,7% dos casos (n = 80) os miomas eram únicos e, na maioria das mulheres, eram de pequenas dimensões, entre os 10 mm e os 19 mm (41,6%, n = 67).

Idades compreendidas entre os 40 e os 59 anos, estado civil casado, excesso de peso, menopausa, anteriores gravidezes e partos ou queixas de menorragia foram associadas a um maior risco para leiomiomas. O uso de contracetivos hormonais combinados foi considerado um factor protetor. Uma vez que, após uma análise multivariada, estas variáveis foram dependentes da idade, podemos sugerir que o envelhecimento é o único fator de risco associado ao aparecimento de miomas uterinos.

Menorragias, metrorragias e dor pélvica foram associadas a um maior risco para miomas múltiplos. O uso de contracetivos hormonais combinados estava mais frequentemente associado a miomas únicos.

Idades compreendidas entre os 40 e os 59 anos, anteriores gravidezes e partos foram associados a uma menor dimensão dos miomas uterinos.

Conclusão: Os miomas uterinos são uma patologia muito comum entre a população feminina. No nosso estudo sugerimos que o único fator de risco relacionado com o desenvolvimento de leiomiomas é o envelhecimento. A gravidez e o parto parecem estar

associados a miomas de pequenas dimensões. Os miomas uterinos únicos são mais comuns em pacientes que utilizam contracetivos hormonais combinados.

Palavras-chave

Mioma uterino, leiomyoma, fibromioma, epidemiologia, ecografia pélvica

Abstract

Introduction: The uterine fibroids are the most common benign neoplasm in the female genital tract. However, the prevalence of this disease in the general population is unknown, which justifies this investigation.

Objective: To evaluate epidemiological factors associated with uterine myomas, in a setting of a private medical clinic.

Methodology: It is presented as a cross-sectional research, drafted with a descriptive and an analytical component.

To collect data a routine demographic computerized file was kept for every patient and a pelvic transvaginal or transrectal ultrasonography was performed. We retrieved from each patient their age at the time of consultation, weight, height, age of menarche, number of pregnancies, pregnancy outcome, marital status, level of education, menstrual cycle and contraceptive method used.

Through the ultrasound examination, we recorded the presence of uterine myomas, their number and the largest dimension of the biggest myoma.

Results: From the total women studied by ultrasonography (n = 624), uterine myomas were documented in 161 (25,8%) cases. Single myomas were presented in 49,7% (n = 80) and the majority of women had small fibroids, between 10 mm to 19 mm (41,6%, n = 67).

Ages between 40 and 59 years, married marital status, overweight, menopause, previous pregnancy and delivery and complaints of menorrhagia were associated with a higher risk for uterine fibroids. The use of combined hormonal contraceptives was found to be a protective factor. Since these variables, after conducting a multivariate analysis, were all age dependent, we can suggest that aging is the only factor associated with the presence of uterine fibroids. Menorrhagia, metrorrhagia and pelvic pain were associated with a higher risk for multiple uterine fibroids. The use of combined hormonal contraceptives was associated with a higher risk for single fibroids. Ages between 40 and 59 years and a history of pregnancy and delivery were associated with a smaller dimension of the leiomyomas.

Conclusion: Uterine myoma is a very common pathology among the female population. In our study, the only risk factor related with uterine fibroids was aging. Pregnacy and delivery seem to be associated with myomas of a smaller dimension. Single myoma is more common in patients using combined hormonal contraception.

Key words

Uterine myoma, leiomyoma, fibroid, epidemiology, pelvic ultrasonography.

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SPSS Statistical Package for Social Sciences
BMI Body Mass Index
IUD Intra Uterine Dispositive
USA United States of America
OR Odds Ratio
OTR Oxytocin Receptor

Introduction

Uterine fibroids, also known as Leiomyoma, originate from the myometrium´s smooth muscle and are the most common benign neoplasm in the female genital tract.

They are sensitive to hormonal stimulation characteristic of the reproductive years. It is known that 20% - 50% of women in this age group suffer from this disease. The uterine fibroids have estradiol receptors levels higher than those found in normal myometrium (1) and have a higher concentration of progesterone receptors A and B in the surrounding myometrium (2), (3).

The uterine myomas are monoclonal (4) and in 40% a chromosomal abnormalities has been described, such as: deletions of the chromosome 7, translocation between chromosome 12 and 14 or trisomy of chromosome 12 (5).

It is known that African women have a greater predisposition to develop this disease (6). Compared with white women, black women develop uterine fibroids at younger ages and they are more numerous and more symptomatic. The prevalence at 50 years was reported to be 59% - 70% in white women and >80% in black women (7), (8). The reasons for this increased susceptibility are not known, but may be associated with estrogen metabolism. A recent study (9) found that the Val/Val genotype of catechol-O-methyltransferase (COMT), an enzyme essential to the metabolism of estrogen, exists in 47% of African women and only in 19% of Caucasian women. This may be one of the reasons for a higher incidence of this disease in this race.

The etiology of uterine fibroids is not yet fully understood, but several risk factors have been identified.

Age seems to be an important factor for developing uterine leiomyoma (10). There is a directly proportional relationship between aging and the development of this disease.

The risk of uterine fibroids appears to be higher in women with an early menarche, especially before 10 years old, compared with women whose menarche occurred after 16 years of age. A possible explanation for this increased risk is the fact that women with early menarche had a premature uterine stimulation with a higher number of muscular cell divisions and a higher probability of having mutations (11). Regular menstrual cycles will also probably facilitate the growth of uterine fibroids (12).

There is no consensus regarding the effect of oral contraception on uterine fibroids development (6, 10, 13-15). A protective effect for leiomyoma is possible in women with prolonged use of oral contraceptives (11).

Another factor described as associated with uterine fibroids is obesity. Reports have shown that, with each increased unit of BMI, the risk of developing this disease increases 6% (13). Another study (10) reported that for each additional 10 kg in weight, the risk of uterine

fibroids rises 21%. The gain of body fat contributes to an increased conversion of androgens into estrogens and thus increases the bioavailability of these, which, as mentioned above, facilitate the growth of uterine fibroids.

Pregnancy seems to protect women from the onset of uterine fibroids (10, 14), reducing both incidence and size. The protective effect is cumulative with the number of pregnancies. A probable explanation is the involution of the uterus after pregnancy, which causes a regression of the blood vessels supplying the myometrium, removing part of the irrigation. This deprives the fibroids of their source of nutrition (15).

During menopause uterine fibroids shrink by the characteristic lack of hormonal stimulation (16). The role of the hormone replacement therapy is controversial. In the study by Palomba et al (17), 74% of women treated with this therapy showed no changes in the size of the fibroid. The study by Polatti et al (18) showed a clear increase in their size during the use of this therapy.

Stewart et al (19) proposed a positive association between tissue damage from pelvic infections and the development of uterine fibroids.

Leiomyomas may be single or multiple. Multiple myomas are the most frequent. Pathologically, they consist of extracellular matrix collagen, fibronectin and proteoglycans. They are covered by a pseudocapsule that demarcates the surrounding myometrium.

The uterine myomas are classified into three categories according to their anatomical location: *Submucous fibroids*, located below the endometrium (occasionally, they develop pedicles or even completely occupy the uterine cavity); *Interstitial / Intramural fibroids*, located within the uterine wall; *Subserous fibroids*, located in the serosal surface of the uterus.

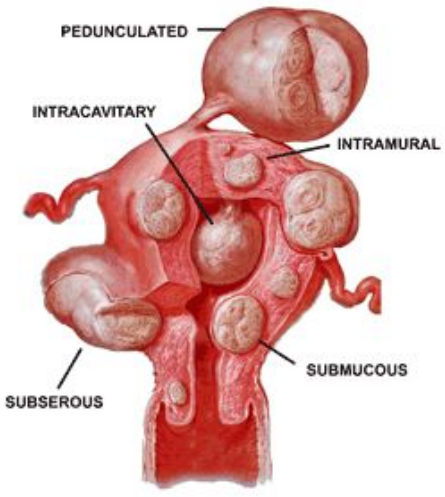

Figure 1: Fibroids classification by their location.(20)

These tumors may develop secondary benign changes such as atrophy, liquefaction, hyalinization, calcification, sepsis, thrombosis or myxomatous degeneration. Malignant transformation into leiomyosarcoma is a rare event (21, 22).

Most women with uterine fibroids are asymptomatic and it was estimated that only 20% to 50% of symptomatic women may attribute their complaints to the fibroid itself (23). The most common symptom of uterine fibroid is abnormal uterine bleeding, especially menorrhagia. In extreme cases, abnormal bleeding can lead to blood loss sufficient to cause iron deficiency anemia. Pelvic pain, urinary symptoms, infertility and miscarriage are other frequent symptoms.

It is difficult to establish an association between abnormal uterine bleeding, such as menorrhagia, and the presence of uterine leiomyomas (24). The Marino et al study (25) did not exhibit any relation between the size, number or location of fibroids and the presence of bleeding. However, the study by Wegienka et al (26) demonstrated that menorrhagia significantly correlates with the size of leiomyomas.

Pelvic pain may be present in cases in which the uterine myoma compresses the surrounding vascular structures; nevertheless, this is an uncommon presentation. Lippman et al (27) found that there is only a slightly higher prevalence of dyspareunia and dysmenorrheal or noncyclic pelvic pain in women with uterine fibroids and they are not related with number or size.

Urinary symptoms, although uncommon, can occur in association with uterine leiomyomas, when they are large enough to compress the neighboring structures of the urinary system (28).

Uterine leiomyomas can lead to reproductive dysfunction. Concerning infertility, there are few studies on this subject, so to draw definitive conclusions more research is needed. Bukulmez and Doody (29) state that 27% of women with uterine fibroids are sterile; however, this correlation depends on the location of the tumor, since intramural and subserosal types do not jeopardize fertility, while submucosal tumors can change it (30-32). Uterine myomas are also implicated in recurrent miscarriages (33, 34) especially in early pregnancy.

To diagnose uterine myomas it is necessary to carry out an accurate clinical history and perform a careful physical examination of the uterus by bimanual palpation. Clinical diagnosis is evident in most cases but must be confirmed with a transvaginal ultrasound (particularly useful in cases of extremely obese patients). Sonohysterography with saline infusion increases the sensitivity in detection of leiomyomas, especially in cases of submucosal fibroids (35-37).

For treatment of uterine leiomyomas several factors should be considered: size, location and characteristics of the fibroids, patient's age, associated symptoms, desire

of future pregnancies and patient's general welfare. Usually, in asymptomatic women, no treatment is required. In symptomatic patients, surgical therapy is the standard approach. If the patient desires to preserve fertility, a myomectomy is preferred. Otherwise, a hysterectomy may be carried out . Medical treatments are indicated for special situations and most of them are still in development.

Although uterine myomas are a frequent pathology and the most important cause of hysterectomy (38, 39), the prevalence of this disease in the general population is unknown.

The aim of this study was to evaluate epidemiological factors associated with uterine myomas, in the setting of a private medical clinic.

Objectives

1) To find out the prevalence of uterine fibroids in the setting of a private medical clinic.

2) To determine demographic and clinical factors associated with leiomyomas.

Methodology

1. Study design

This was a retrospective, descriptive and transversal study. This study favored a quantitative approach, because it aims to collect and process the data in a systematic and statistical way, establishing relationships between variables in order to meet the objectives of the investigation.

2. Sample

The sample consists of all the women consecutively attended in a gynecological consultation in a private clinic, in Covilhã, Portugal, from January 2 until December 31, 2010.

The same gynecologist, with more than 20 years of gynecological practice, attended all patients.

Were excluded from the study those patients previously submitted to hysterectomy and women pregnant at the time of consultation.

All patients were Caucasian with the exception of three African women.

3. Data Collection

Data collection was done through the systematic analysis of clinical processes. By routine, demographic data from every patient was recorded in a standard file. In all cases a pelvic transvaginal or transrectal ultrasonography was performed. The sonographic device used was the TOSHIBA Memio 17, SSA-550A. The endovaginal probe used was the TOSHIBA PVM 651VT 6MHz.

We collected data on 624 patients and from each case the following variables were selected for analysis: the age of the patient at the moment of consultation, weight, height, age of menarche, number of pregnancies, pregnancy outcome deliveries, marital status, level of education, menstrual cycle and contraceptive method. Through the ultrasound examination, we could record the presence, number and largest dimension of the biggest uterine myoma.

4. Statistical Methodology

The data was organized and analyzed in Statistical Package for Social Sciences ® (SPSS – version 17.0 for Windows).

Initially we used the descriptive statistics in order to explore the available information. Later we resorted to statistical inference with the aim of characterizing the relationship between the variables being studied. In particular, we used Pearson Chi-Square Test for the purpose of studying possible relations of dependence. In all cases, a p-value <0,05 was considered significant.

Results

1. Descriptive analysis

1.1) Sample characterization

We studied 624 women. The mean age was 39.62 years and the standard deviation is 12.580.

Table 1. Descriptive analysis of the variable *age*.

Variable	Minimum	Maximum	Mean	Std. Deviation
Age	15	77	39,62	12,580

Figure 2 shows the distribution of the sample by age. Most patients had between 20 and 39 years (49,5%, n = 309). Few patients were less than 20 years-old (1,9%, n = 12).

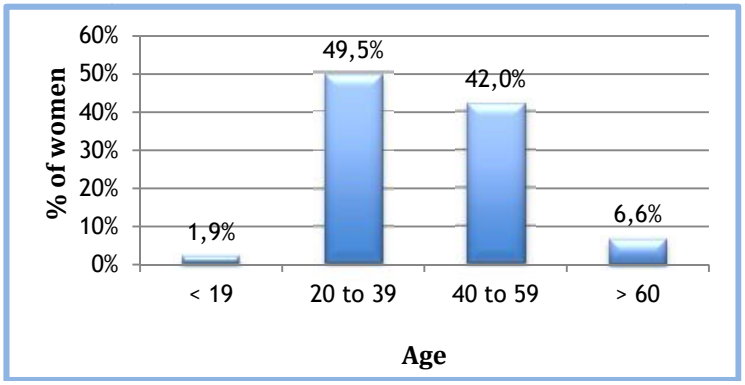

Figure 2. Graphical representation of the sample´s age.

Three hundred and four women (63,1%) had an education level of high-school or less and 36,9% (n = 230) had college or more.

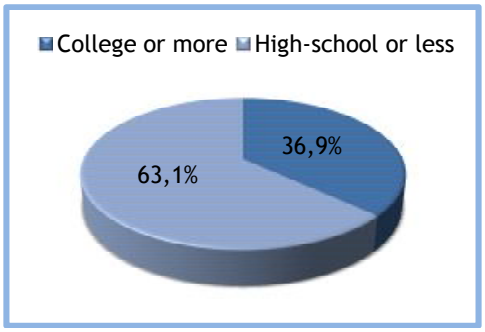

Figure 3. Graphical representation of the sample's level of education.

Most women, 66,2% (n = 413), were married. The remainder 33,8% (n = 211) were single, widowed or divorced.

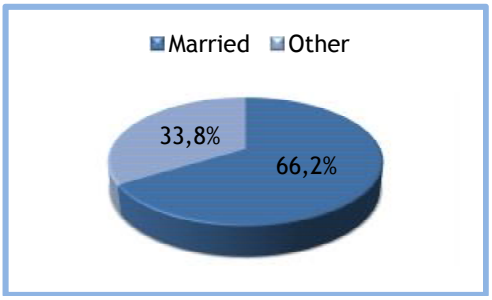

Figure 4. Graphical representation of the sample's marital status.

Most women (59,5%, n = 370) were within the normal range of Body Mass Index (18,5 to 24,9) and 27,1% (n = 169) were overweight, with a BMI between 25 and 29,9. Sixty four women (10,3%) had a BMI over 35 and only 3,4% (n = 21) had a low weight (BMI less than 18,5).

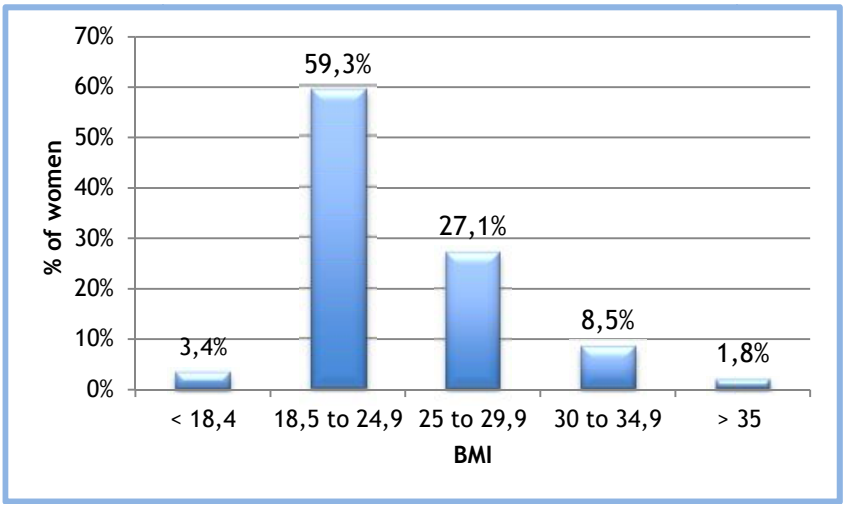

Figure 5. Graphical representation of the sample´s Body Mass Index.

Mean age of menarche was 12,6 years. Half of the patients reported menarche age before 13 year.

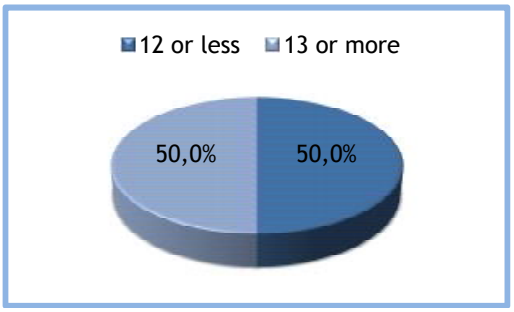

Figure 6. Graphical representation of the sample´s age of menarche.

At the time of the consultation, 16,2% of the women (n = 101) were postmenopausal. The others were premenopausal women.

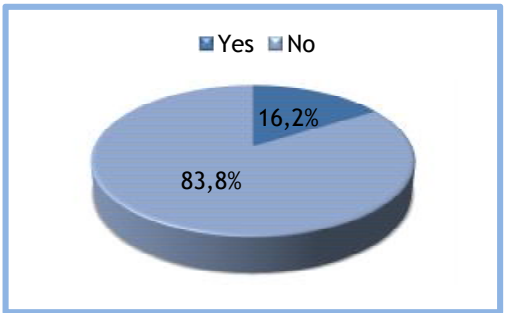

Figure 7. Graphical representation of the sample´s menopausal status.

As seen in figures 8 and 9, 31,7% (n = 198) of the patients had never been pregnant and 35,7% (n = 223) never had a delivery.

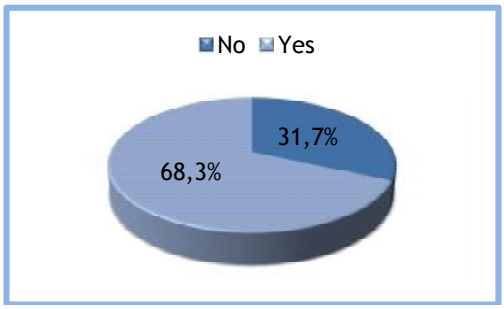

Figure 8. Graphical representation of the sample´s history of pregnancy.

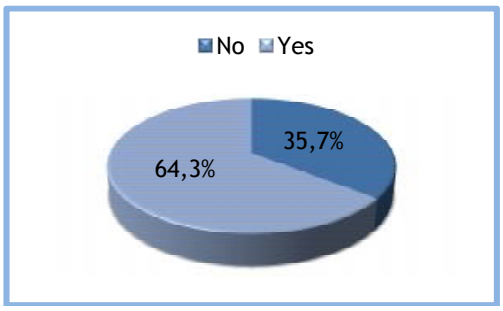

Figure 9. Graphical representation of the sample's history of delivery.

It was seen that 25% (n = 156) of women had one pregnancy and 26,1% (n = 163) had two pregnancies, while 26,1% (n = 163) had one delivery and 38,1% (n = 238) had two or more deliveries.

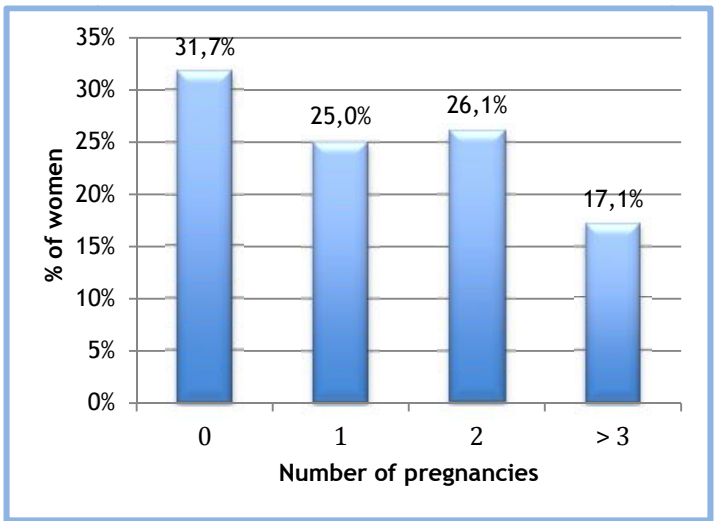

Figure 10. Graphical representation of the sample´s number of pregnancies.

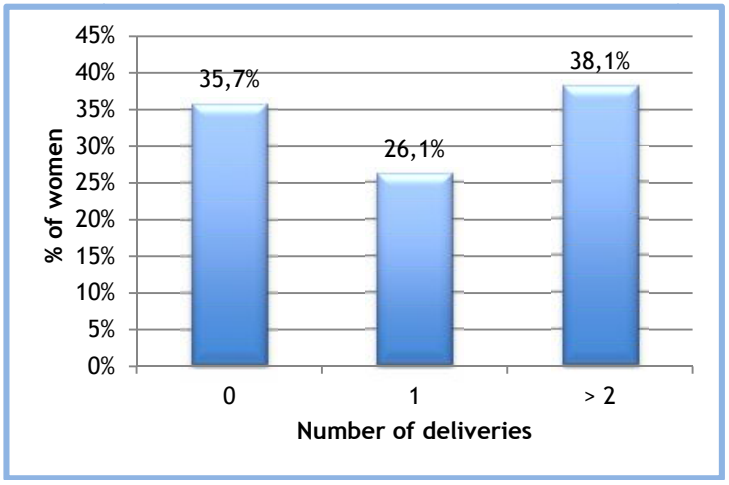

Figure 11. Graphical representation of the sample´s number of deliveries.

Between the women who have been pregnant, 14.7% (n = 92) had at least one miscarriage.

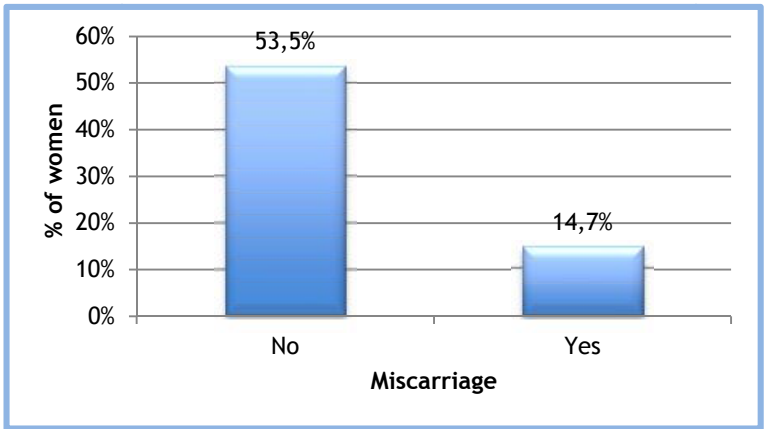

Figure 12. Graphical representation of the sample's history of miscarriage.

Between the women who already had a delivery, 12,5% (n = 78) had at least one cesarean incision.

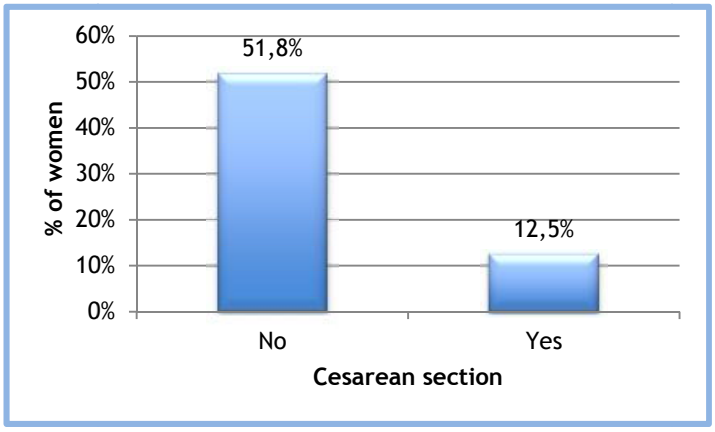

Figure 13. Graphical representation of the sample's history of cesarean section.

Twenty five women (4%) were not sexually active.

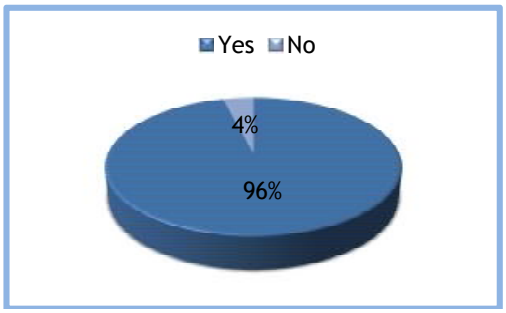

Figure 14. Graphical representation of the sample's sexual activity.

Among the sexually active women, 34,4% (n = 206) were using combined pill at the moment of consultation and 56,6% (n = 339) were using the IUD or other non-hormonal method, including no contraception. Only 9,0% (n = 54) were using a hormonal method with progestatives alone.

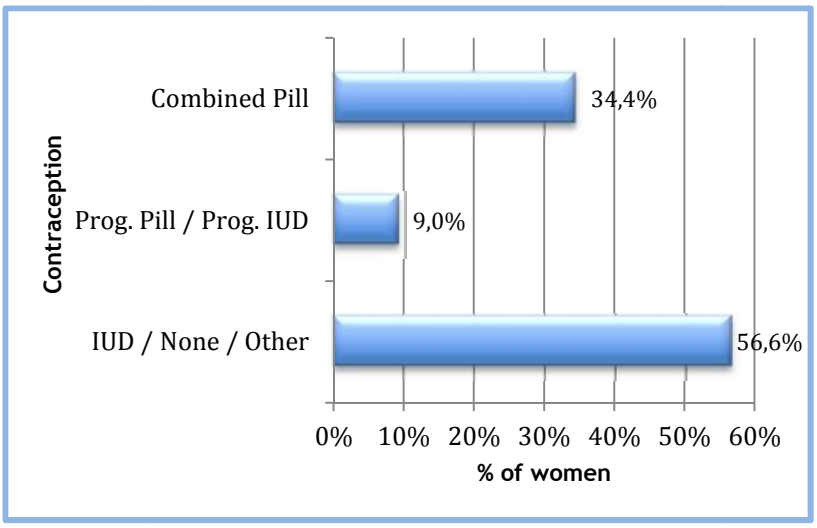

Figure 15. Graphical representation of the sample's contraceptive method used.

Twenty nine women were infertile, which corresponds to 5% of the sexually active women.

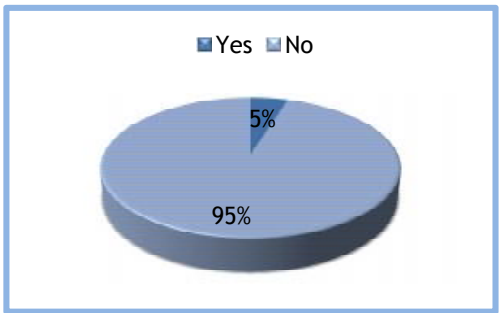

Figure 16. Graphical representation of the sample's history of infertility.

Most women sought consultation as a routine check-up (31,6%, n = 197). The most frequent complaint, consisting of 18% (n = 113) of the women, was menstrual disorders such as dysmenorrhoea, menorrhagias and metrorrhagias (the most frequent, appearing in 10,9% of the women, n = 68). Other common symptoms include those from the vulva like vulvar pain and pruritus (9,6%, n = 66).

Sixty one women (9,8%) had pelvic symptoms, which include pelvic pain or pelvic relaxation.

Breast symptoms like pain or lumps were the main reason 7,5% (n = 47) of the women came to the consultation.

Five percent of the women (n = 31) sought consultation for contraception counseling, 3,4% (n = 21) for infertility counseling and 1,1% (n = 7) had sexual disorders like dyspareunia.

There were other reasons for women to seek consultation, like menstrual headaches (0,5%, n= 3), coitorragias (2,9%, n = 18), leucorrhea (5,8%, n = 36), endometrial thickening (0,3%, n = 2), climacteric symptoms (1,9%, n = 12), abnormal cytology (1,4%, n = 9), urinary disorders (1%, n = 6) and ovarian tumor (0,2%, n = 1).

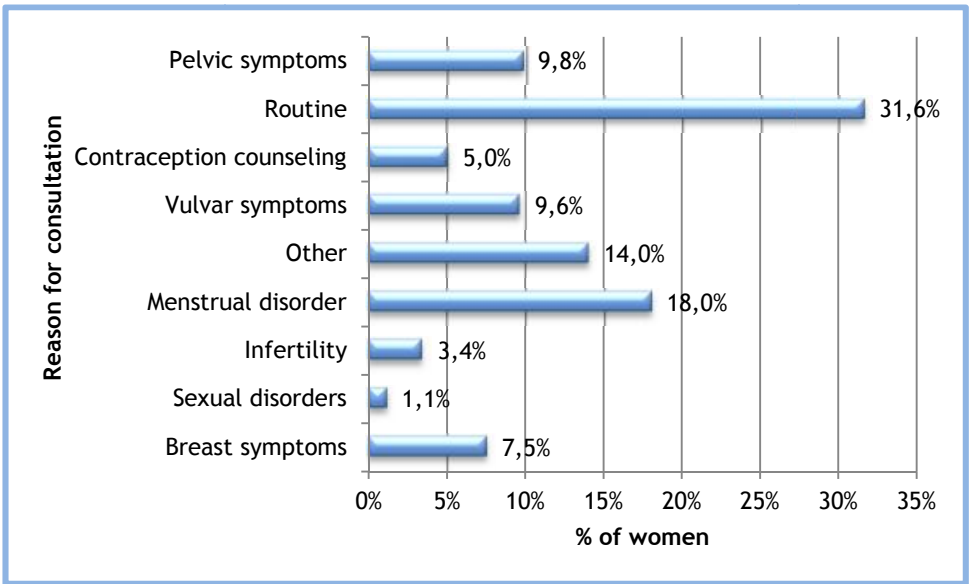

Figure 17. Graphical representation of the sample´s reason for seeking consultation.

At gynecological examination no abnormality was found in 45,2% (n = 282) of the women, but in 17% (n = 106) uterine enlargement was diagnosed.

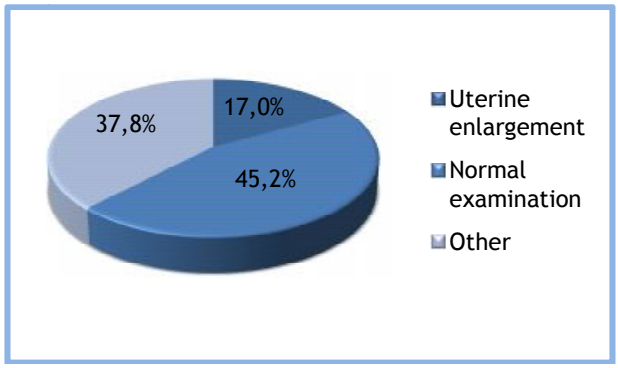

Figure 18. Graphical representation of the sample's result at gynecological examination.

In 161 patients (25,8%) uterine myomas were documented by ultrasonography. Single myomas were found in 49,7% of the cases (n = 80) and multiple myomas were found in 50,3% of the cases (n = 81).

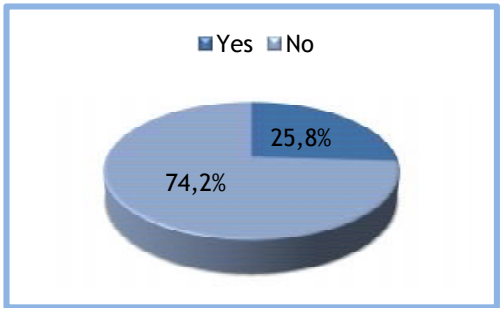

Figure 19. Graphical representation of the sample´s presence of uterine fibroids on ultrasound.

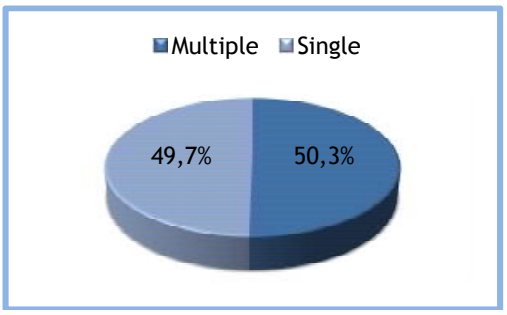

Figure 20. Graphical representation of the sample's number of uterine fibroids on ultrasound.

The majority of the women had small fibroids, between 10 mm to 19 mm (41,6%, n = 67) or between 20 mm to 29 mm (26,7%, n = 43). Only 6,2% (n = 10) had uterine myomas with more than 50 mm.

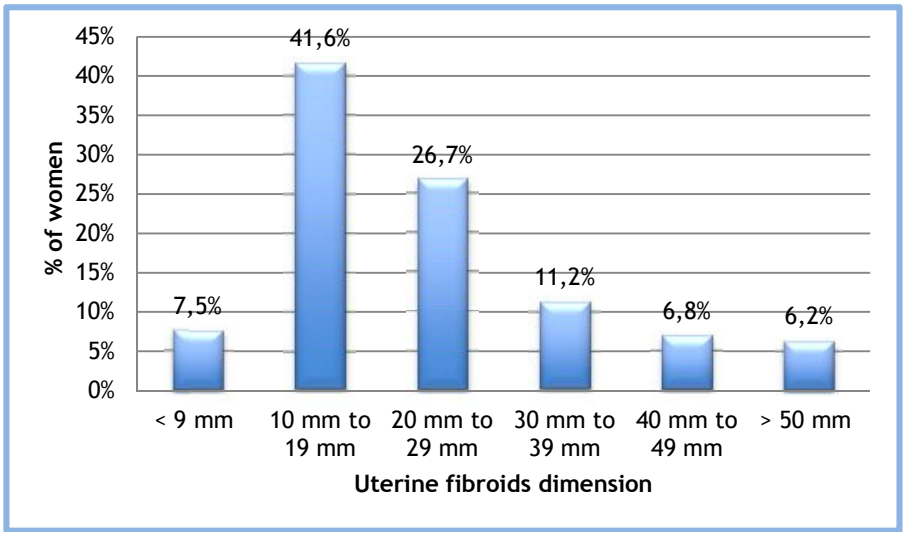

Figure 21. Graphical representation of the sample´s dimension of the biggest uterine fibroid on ultrasound.

The patients with leiomyomas had previous knowledge of the disease in 61,5% of the cases (n = 99).

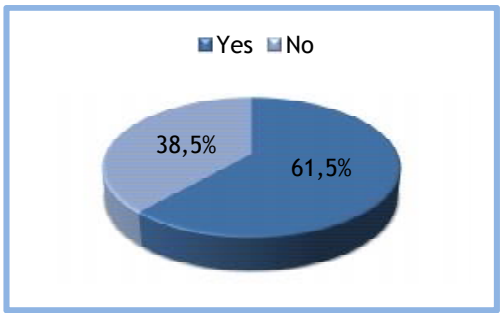

Figure 22. Graphical representation of the sample's previous diagnosis of uterine fibroids.

2. Statistical Inferences

2.1) To evaluate the relationship between the presence of fibroids on the ultrasound and the different variables:

Table 2 shows the significant variables for the diagnosis of uterine fibroids by ultrasonography.

Table 2. Statistically significant relationship between diagnose of leiomyoma on ultrasound and the different variables.

Variable		Leiomyoma on ultrasound		*p* value
		No	Yes	
Age	19 or less	100,0%	0,0%	0,0001
	20 to 39	89,0%	11,0%	
	40 to 59	54,6%	45,4%	
	60 or more	80,5%	19,5%	
Marital status	Married	69,2%	30,8%	0,0001
	Other	83,9%	16,1%	
BMI	18,4 or less	85,7%	14,3%	0,002
	18,5 to 24,9	79,2%	20,8%	
	25 to 29,9	66,9%	33,1%	
	30 to 34,9	62,3%	37,7%	
	35 or more	54,5%	45,5%	
Menopause	No	76,1%	23,9%	0,011
	Yes	64,4%	35,6%	
Pregnancy	No	89,4%	10,6%	0,0001
	Yes	67,1%	32,9%	
Delivery	No	87,4%	12,6%	0,0001
	Yes	66,8%	33,2%	
Contraception	Combined Pill	85,9%	14,1%	0,0001
	IUD or other	69,6%	30,4%	
	Progestative IUD or Progestative Pill	70,4%	29,6%	
Presenting symptom	Menorrhagia	26,7%	73,3%	0,0001
	Menstrual disorder	70,4%	29,6%	
	Metrorrhagias	63,2%	36,8%	
	Other	78,8%	21,2%	
	Pelvic pain	64,3%	35,7%	

Women with ages between 40 and 59 years, married, overweighed, postmenopausal, those who had already been pregnant, who had at least one delivery or complained of menorraghia had a higher risk of presenting with uterine fibroids on the ultrasound.

The use of combined hormonal contraceptives was considered a protective factor for this condition.

We failed to demonstrate the existence of a significant correlation between the level of education, age at menarche, number of pregnancies and deliveries, history of miscarriage or cesarean and the presence of leiomyoma on the ultrasound.

Table 3. Not statistically significant relations between diagnose of uterine fibroids on ultrasound and the different variables.

Variable		Leiomyoma on ultrasound		*p* value
		No	Yes	
Scholarity	College or more	77,0%	23,0%	0,134
	High school or less	72,6%	27,4%	
Age at menarche	12 or less	74,0%	26,0%	0,500
	13 or more	74,4%	25,6%	
Number of pregnancies	1	65,4%	34,6%	0,741
	2	69,3%	30,7%	
	3 or more	66,4%	33,6%	
Number of deliveries	1	63,2%	36,8%	0,120
	2 or more	69,3%	30,7%	
Miscarriage	No	68,6%	31,4%	0,143
	Yes	62,0%	38,0%	
Cesarean	No	66,3%	33,7%	0,360
	Yes	69,2%	30,8%	

In table 4 are shown the results of a multivariate analysis encompassing the significant variables for risk of leiomyoma. After adjustment, aging is the only factor with statistical significance associated to ultrasonography diagnosis of uterine fibroid.

Table 4. Relation between the age and the remaining variables.

Variable	***p* value**
Marital status * Age	**0,0001**
BMI * Age	**0,0001**
Menopause * Age	**0,0001**
Pregnancy * Age	**0,0001**
Delivery * Age	**0,0001**
Contraception * Age	**0,0001**
Presenting symptom * Age	**0,0001**

2.2) To evaluate the relationship between the number of fibroids on the ultrasound and the different variables:

In table 5 are shown the significant variables for number of leiomyomas diagnosed by ultrasonography.

Table 5. Statistically significant relations between the number of uterine fibroids on ultrasound and the different variables.

Variable		Leiomyoma number		*p* value
		Multiple	Single	
Contraception	Combined Pill	27,6%	72,4%	0,033
	IUD or other	52,5%	47,5%	
	Progestative IUD or Progestative Pill	68,8%	31,3%	
Presenting symptom	Menorrhagia	72,7%	27,3%	0,011
	Menstrual disorder	12,5%	87,5%	
	Metrorrhagias	72,0%	28,0%	
	Other	44,3%	55,7%	
	Pelvic pain	55,0%	45,0%	

Women whose main complaint at the consultation was menorrhagia, metrorrhagia or pelvic pain had a higher risk of presenting with multiple uterine fibroids on the ultrasound.

Single uterine fibroids were diagnosed more frequently in women on combined hormonal contraceptives.

We failed to demonstrate the existence of a significant correlation between age, marital status, BMI, menopause, pregnancy or delivery and the number of leiomyomas on the ultrasound.

Table 6. Not statistically significant relations between the number of uterine fibroids on ultrasound and the different variables.

Variable		Leiomyoma number		*p* value
		Multiple	Single	
Age	19 or less	0,0%	0,0%	0,057
	20 to 39	32,4%	67,6%	
	40 to 59	54,6%	45,4%	
	60 or more	62,5%	37,5%	
Marital status	Married	49,6%	50,4%	0,440
	Other	52,9%	47,1%	
BMI	18,4 or less	0,0%	100,0%	0,449
	18,5 to 24,9	49,4%	50,6%	
	25 to 29,9	53,6%	46,4%	
	30 to 34,9	55,0%	45,0%	
	35 or more	40,0%	60,0%	
Menopause	No	48,8%	51,2%	0,300
	Yes	55,6%	44,4%	
Pregnancy	No	47,6%	52,4%	0,488
	Yes	50,7%	49,3%	
Number of pregnancies	1	51,1%	48,9%	0,912
	2	53,1%	46,9%	
	3 or more	55,9%	44,1%	
Delivery	No	50,0%	50,0%	0,568
	Yes	50,4%	49,6%	
Number of deliveries	1	48,3%	51,7%	0,400
	2 or more	52,1%	47,9%	

2.3) To evaluate the relationship between fibroids of larger dimensions on the ultrasound and the different variables:

In table 7 are shown the significant variables for the different leiomyomas dimensions on ultrasonography.

Table 7. Statistically significant relation between the dimension of uterine fibroids on ultrasound and the different variables.

Variable		Leiomyoma dimension		*p* value
		< 30 mm	> 30 mm	
Age	19 or less	0,0%	0,0%	**0,030**
	20 to 39	88,2%	11,8%	
	40 to 59	71,4%	28,6%	
	60 or more	87,5%	12,5%	
Pregnancy	No	47,6%	52,4%	**0,001**
	Yes	80,0%	20,0%	
Delivery	No	57,1%	42,9%	**0,003**
	Yes	79,7%	20,3%	

Ages between 40 and 59 years and a history of pregnancy and delivery were significantly associated with smaller leiomyomas on the ultrasound.

We failed to demonstrate the existence of a significant correlation between the marital status, BMI, menopause, number of pregnancies or deliveries, contraceptive method used and documented symptoms at the initial consultation with the dimension of uterine myomas on ultrasound.

Table 8. Not statistically significant relations between the dimension of uterine fibroids on ultrasound and the different variables.

Variable		Leiomyoma dimension		*p* value
		< 30 mm	> 30 mm	
Marital status	Married	78,0%	22,0%	0,520
	Other	67,6%	32,4%	
BMI	18,4 or less	100,0%	0,0%	0,653
	18,5 to 24,9	74,0%	26,0%	
	25 to 29,9	73,2%	26,8%	
	30 to 34,9	80,0%	20,0%	
	35 or more	100,0%	0,0%	
Menopause	No	74,40%	25,60%	0,479
	Yes	80,56%	19,44%	
Number of pregnancies	1	85,2%	14,8%	0,174
	2	68,0%	32,0%	
	3 or more	88,9%	11,1%	
Number of deliveries	1	80,0%	20,0%	0,317
	2 or more	79,5%	20,5%	
Contraception	Combined Pill	96,6%	3,4%	0,084
	IUD or other	68,8%	31,3%	
	Prog. IUD or Prog. Pill	62,5%	37,5%	
Presenting symptom	Menorrhagia	72,7%	27,3%	0,369
	Menstrual disorder	75,0%	25,0%	
	Metrorrhagias	60,0%	40,0%	
	Other	80,2%	19,7%	
	Pelvic pain	75,0%	25,0%	

Discussion

Our study showed that the prevalence of uterine fibroids on 624 Caucasian women in a private clinic in Covilhã, Portugal, was 25,8%. This result is in agreement with the study published by Marino et al (25), in the USA, which found a prevalence of 21,4% of uterine fibroids on ultrasound in a sample of 341 women aged between 30 to 60 years. By analyzing a sample of 4714 myomectomies and personal records of 59 cases Buttran et al (40) also found that 20% - 25% of women develop uterine fibroids myomectomies. Other studies have shown a lower prevalence of uterine fibroids in Caucasian populations, as is the case of Borgfeldt et al (41), who found on ultrasound uterine fibroids in 5,4% of women in a sample of 335 women between 25 and 40 years. We attribute these differences to the small sample of the study in question and the small range of age groups included, since it does not consider patients over 40 years.

Other studies demonstrate prevalence rates of uterine fibroids greater than those observed by us, as that of Cramer et al (42), who found a prevalence of 77% in the anatomopathological examination of a sample of 100 total hysterectomy specimens. We attribute these differences to the methodology and to the fact that the anatomopathological exam has a higher sensitivity compared to ultrasonography.

We observed a conservative attitude by the physicians concerning this disease, since 61,5% of the patients with leiomyomas were aware of their conditions but did not remove them.

In general, most studies have found an increased incidence of uterine fibroids with advancing age (10). Our study found that women with fibroids were most likely to be between 40 and 59 years (45,4%). This result is in agreement with other studies, in particular the one published by Chen et al (43), a case-control study with a sample of 317 women aged between 17 and 44 years with uterine fibroids at the time of tubal sterilization or who reported a history of uterine fibroids. By using unconditional logistic regression separately for White and African-American women, it observed that ages between 40 and 44 years are a risk factor for the development of leiomyomas in white women (OR = 6.3, 95% confidence interval).

Previous studies have mentioned an association between marital status and the presence of uterine fibroids on ultrasound, as in the case control study conducted by Choi et al (44), where the prevalence of uterine fibroids was determined by ultrasound and a statistically significant correlation was found. We also found that there was a major prevalence of uterine fibroids in married women (30,8%) compared with non-married (16,1%). Other studies have shown results conflicting with those obtained by us, as is the case of Novak

et al (45), that found a higher incidence of uterine fibroids in single women. Olantiwo et al (46) state that marital status does not appear to affect the incidence of uterine fibroids. These differences may be justified by the fact that in our sample the majority of women are married, which may alter the results.

In our study we observed that there is a statistically significant association between the BMI and the prevalence of leiomyomas, since overweight women (BMI > 24,9) had a higher prevalence of this disease.

Previous studies on this subject have shown conflicting results. Samadi et al (47) a case-control study with 201 women with uterine fibroids and 1503 women without this pathology, observed that the incidence was lower in women with lower BMI. Parazzini et al (48), a case-control study in the Greater Milan area with 275 women with fibroids and 722 controls, found that there was no statistically significant association between BMI and the incidence of these. The study of Shikora et al (49) showed that the majority of women with leiomyomas were obese.

Our study found a higher prevalence of uterine fibroids in postmenopausal women, this inference being statistically significant. These results are not in accordance with those observed by Cramer et al (42), who reported that these patients have less fibroids. This same study also states that in these patients the fibroids are smaller, different results from those obtained by us, since we found that in postmenopausal women 55,6% of fibroids are multiple.

Cramer et al (50) found that small myomas from postmenopausal women had significantly smaller cell sizes than did size-matched myomas from age-matched premenopausal women. In our study, we could not find any statistically significant association between menopause and the leiomyoma size.

In a statistical univariate analysis, we observed a statistically significant association between pregnancy and the onset of uterine fibroids. We also observed a similar relationship with regard to delivery. In both cases, approximately 80% of the fibroids found on ultrasound were small fibroids (less than 30 mm). However, after adjustment, no significance was documented. Baird et al (51) found that after each pregnancy, during the rapid remodeling of the uterus, smaller fibroids will eventually be eliminated, hence the lower prevalence of this disease in women who had been pregnant. Also, Cesen et al (52), in a study with animal models, found that the Oxytocin Receptor (OTR), expressed by the cells of leiomyomas, appears to inhibit the pathway of estrogen-induced cell proliferation, thereby mediating the protective effect of pregnancy and delivery in this pathology.

Our study noted that patients who were using combined hormonal contraceptives had a lesser prevalence of uterine fibroids (14,1%) and that 72,4% presented with single myomas. We conclude that hormonal contraceptive methods prevent the development of uterine

fibroids. These results are in agreement with Chiaffarino et al (53), who found that, on a sample of 843 women in which 30,1% used oral contraception, there was no association between their use and the risk of fibroids. Therefore they concluded that these should not be contraindicated in cases of uterine fibroids.

We concluded that the women using progestive alone contraceptive methods have approximately the same prevalence of this disease when compared with women who did not use any hormonal contraception method (30%). These results are not consistent with those obtained by Wise et al (54), in a prospective cohort study conducted in the USA, with a sample of 22.895 premenopausal African-American women, which concluded that Progestin-only injectables may reduce the risk of uterine fibroids.

Parazinni et al (55), in a case-control study conducted in Italy with a sample of 390 women under 55 years, failed to establish any direct association between the use of oral contraceptives and the presence of uterine fibroids.

In our study we concluded that 29,3% of patients with uterine fibroids experience no symptoms, which is consistent with the current literature, such as the studies by Cramer et al (42) and Buttram et al (40) , who reported that most women with uterine fibroids are asymptomatic.

We observed that leiomyomas were discovered on ultrasound in 73,3% of the women with menorrhagias and that 72,7% of them were multiple. Stewart et al (56) also states that the most characteristic bleeding pattern of uterine fibroids is heavy flow.

In 13,6% of women with uterine fibroids, pelvic symptoms were the prevalent complaints, including pain due to the compression performed by the myoma's mass. Grover et al (57), in a study with a sample of 2623 asymptomatic women, detected a bulky uterus or fibroids in 12,9% of women, somewhat similar to the percentage found by our study.

As mentioned above, several studies claim that there is an association between the presence of uterine leiomyomas and the development of reproductive dysfunction, including infertility. An article published by the American Society of Reproductive Medicine (58) concluded that uterine myomas are associated with this disorder in 5% to 10% of patients. In our study, 1,3% of women with uterine fibroids presented complaints of infertility.

Ortiz et al (59), in a case-control study with 65 pregnant patients with uterine fibroids and 165 pregnant patients without them, found a higher risk of miscarriage in patients with this disease.

Olive et al (60) found that submucous myomas increase miscarriage rates; intramural and subserosal myomas may also increase these rates.

In our study, however, we could not find any statistically significant association between miscarriage and uterine myomas.

We also could not find any statistically significant association between the cesarean delivery and uterine myomas. Ortiz et al (59) also did not found any significant differences in the frequency of cesarean section between women with or without leiomyomas. Olive et al (60), on the other hand, found an increased risk of cesarean delivery in women with uterine fibroids.

Several studies claim an association between the early age of menarche and the incidence of uterine myomas (6, 61). In our study, however, we could not find any statiscally significant association between these two.

After a multivariated analysis, we concluded that all the variables were age-dependent, so we suggest that aging is the only factor that can be associated with the development of uterine myomas.

Strengths and Limitations

This study has some unique particularities: 1) this is one of the studies about uterine fibroids with the largest sample; 2) it includes all women sequentially; 2) diagnosis of uterine myoma was made by ultrasonography, which is a good sensitive test method; 3) data was collected by a single observer; 4) a standard computerized demographic file was routinely used for all women.

However, some limitations should be considered: 1) the data was collected by a single observer, with risk of subjective bias; 2) the fact that this is a cross-sectional study does not allow perceiving the variations of the different variables through time; 3) the studied sample was economically more privileged and more cultured than the ordinary population living in Covilhã.

Conclusion

The results of this study are similar to those obtained in other publications regarding the increased prevalence of uterine leiomyomas with .aging.

We conclude that there is a directly proportional relationship statistically significant between age, married marital status, overweight, pregnancy, menopause, childbirth and the presence of menorrhagia and an increased prevalence of uterine fibroids, all of which are risk factors for the development of this condition.

Regarding hormonal contraceptive methods, we concluded that there is a statistically significant inverse relationship between their use and the increased prevalence of uterine myomas; Indicating that hormonal contraceptives are a protective factor for this condition.

We conclude that there is a directly proportional relationship statistically significant between the presence of menorrhagia, metrorrhagia and pelvic pain and an increased prevalence of multiple uterine fibroids. The use of combined hormonal contraceptives showed a directly proportional relationship statistically significant with the presence of single fibroids.

Age, pregnancy and delivery were associated with the diagnosis of smaller leiomyomas.

We were unable to find any statistically significant association between the educational level, age at menarche, number of pregnancies, miscarriages, cesarean sections and the prevalence of uterine fibroids.

We suggest that the only risk factor to uterine fibroids is age, since all of the variables were age-dependent.

Based on our results, we think that it is important to inform all patients with the diagnosis of uterine myoma that:

1. It is a frequent benign disease (25,8% of the women, in our study);
2. The prevalence increases with aging (in our study no other factors were documented);
3. Most of the patients with leiomyoma live well with their pathology (in our study, 61,8 % of the women had previous knowledge of the disease);

4. The main complaint associated with the diagnosis of leiomyoma is menorrhagia (in our study, 73,3% of the women with menorrhagias had this diagnosis);
5. The best clinical attitude should be first: to inform; second: to reassure the patient; and third: to treat the patients exhibiting symptoms.

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