ORIGINAL ARTICLE

# THE IMPACT OF UTERINE FIBROMATOSIS ON THE ENDOMETRIUM AND FERTILITY

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## Abstract

*Uterine fibroids are the most common benign tumor that can be found in a woman's reproductive system. The uterine fibroid affects millions of women globally each year and we can consider this pathology, without exaggerating, an important public health problem. Our study was carried out prospectively, in 5 years (2015-2019) and enrolled 480 patients selected with uterine fibroid, from a number of 28809 women who were hospitalized during this period in the university clinic of Obstetrics and Gynecology within the „Saint Pantelimon" Emergency Hospital, Bucharest, Romania. Patients were divided into two groups of study: Group A, those with well-defined, single or multiple uterine fibroid and Group B – patients with diffuse uterine fibromatosis. The clinical, histopathological and immunohistochemical study analyzed and monitored over time, by comparison between the two groups, 52 parameters for each patient, starting with the usual epidemiological factors (age, weight, height, body mass index, personal or family medical history, etc.), continuing with those related to fertility and other clinical issues (chronic pain, metrorrhagia, number of births, recurrent miscarriage, etc.), up to intraoperative parameters (duration of surgery, blood loss, pelvic drainage, the need for blood transfusion) and finally, histopathological aspects. We present in this article some of the results of our study, those related to the quality of the endometrium in the fibromatous uterus and the influence that uterine fibroid had on the fertility of our patients.*

**Keywords***: uterine fibroid, endometrium in fibromatosis, fertility, sterility*

## Introduction

Uterine fibroids occur in general at 20-25% of women and almost 45-50% of them who are over 45 years old and still have menstruation [1]. The prevalence of fibroid is variable, it increases linearly with age throughout the reproductive period of women, reaching a peak between the ages of 45-49 years old (6.3 per 1,000 people/year), then the tendency is to decrease in postmenopause [2]. As we have found, the incidence of uterine fibroid is very variable in the literature. Starting from the highest figures as described in some studies, between 20 - 40% in the group ages of 40-45 and 45-50 years old, the incidence decreases as the group studied is larger

and the diagnosis more accurate [2,3]. The effects of fibroids on the endometrium have been simplistic entrusted for a several periods of time, as due to the size and the possible position of these tumors in the muscular wall of the uterus. The perspective has changed as the mechanisms of pathophysiology and genetic control of the cellular level, from the extracellular matrix as well as the intercellular signaling mechanism, were better understood. Some studies have shown that uterine fibromatosis influences paracrine expression of some endometrial genes and expression of some local receptors. The quality of the endometrium is directly affecting the fertility of patients through the ability of implantation and sustainability of a pregnancy.

## Materials and Methods

Our study, lasting for a period of 5 years (2015-2019), was carried out prospectively and enrolled 480 patients selected from a number of 28809 women who were hospitalized during this period in the university clinic of Obstetrics and Gynecology within the „Saint Pantelimon" emergency hospital, Bucharest, Romania. The 480 patients were classified into two groups of study according to the clinical data, imaging and then, postoperative, based on macroscopic and microscopic appearance in: group A - 300 patients with well-defined uterine fibroid, single or multiple with the size of the smallest node over 1 cm and group B - 180 patients with diffuse uterine fibromatosis, without obvious nodules or in which microscopic fibromatous nodules were described at the anatomopathological examination. Depending on the appearance of the uterus, both intraoperative and postoperative, and especially on the basis of the final histopathological diagnosis, the patient was reassigned to the appropriate cohort when the initial ultrasound diagnosis was not consistent with the reality [4].

The inclusion criteria in the study were: patients diagnosed with fibroid or diffuse fibromatosis clearly established clinically and imaging; patients with severe symptoms as: metrorrhagia, anemic syndrome, severe or chronic abdominal pain, urinary or sexual dynamics disorders, fertility disorders [4]. Also included were patients with moderate but unimproved symptoms under chronic drug treatment and who agreed in write with the surgery. For a better equability of obtaining histological data, especially of those in which endometrium was analyzed - all patients included in the study, were in the early or middle secretory phase of the menstrual cycle, except of those in menopause. The exclusion criteria were: previously diagnosed endometrial hyperplasia, cervical or endometrial neoplasms and sarcomas, which have completely different therapeutic management protocols than uterine fibromatosis. Also, patients who recently were treated with COCs, progesterone or GnRh agonists, were excluded. We also excluded, for a more accurate comparison of the two cohorts, patients in whom the final histopathological examination, obtained postoperative (by hysterectomy, myomectomy or in some cases, by myometrectomy) showed a mixed appearance with uterine fibroid (myoma) well delimited but also diffuse uterine fibromatosis. The clinical, histopathological and immunohistochemical study analyzed and monitored over time 52 parameters in each patient, in the two groups of study, starting with the usual epidemiological factors (age, weight, height, body mass index, personal or family medical antecedents, etc.), continuing with those related to fertility (births, recurrent miscarriages, pregnancy loss rate, etc.) and up to intraoperative parameters (duration of surgery, blood loss, pelvic drainage), histopathological (endometrium, particular aspects of the myometrium) and immunohistochemical. There is to mention that the clinical study has ended and that immunohistochemical database is being processed. The final, complete results, will be included in a doctoral thesis and will be published later.

## Results

The two groups of selected patients were not equal, the first group (A) included 300 patients with single or multiple uterine fibroids and in the second group (B), with diffuse uterine fibromatosis, with a slightly rarer frequency in the clinic, we managed to recruit 180 patients to meet the inclusion criteria. Mean age, mean weight, and body mass index (BMI) were comparable in the two groups (Table 1). In

contrast, significant differences were observed in terms of the average size of the uterus (Table 1) and its volume.

| Patients | Group A (300 Pac.) | Group B (180 Pac.) |
|---|---|---|
| Avg. age | 46,73 years | 48,75 years |
| Avg. weight | 76,64 kg | 74 kg |
| BMI | 27,23 kg/m² | 27,12 kg/m² |
| Avg. size of the uterus | 12/9,02/6,79 cm | 10,2/7,9/6,3 cm |

**Table 1 – Epidemiological parameters**

Symptomatology and clinical data were compared and differences were noted (Table 2), especially in terms of dysmenorrhea, dyspareunia and the feeling of pelvic fullness, the latter being explained by the much higher average volume of the uterus of patients in group A (Figure 1). Pain and dysmenorrhea were self-assessed by patients on a simple numerical scale, where 0 means no pain, 1-3: minimal pain, 4-7 moderate pain, and 8-10 severe pain. The concordance between the ultrasound and the histopathological diagnosis was 94.6% in group A and 91.6% respectively in group B.

| Symptoms | Group A | Group B |
|---|---|---|
| 1. Chronic pain | 191 (63,66%) | 106 (58,88%) |
| 2. Dysmenorrhea | 171 (57,33%) | 78 (43,33%) |
| 3. Metrorrhagia | 225 (74,66%) | 129 (71,66%) |
| 4. Feeling of fullness | 123 (41%) | 38 (21,11%) |
| 5.Urinary incontinence | 48 (16%) | 29 (16,11%) |
| 6. Dyspareunia | 158 (52,66%) | 73 (40,55%) |

**Table 2 – Symptoms: comparison between the two groups**

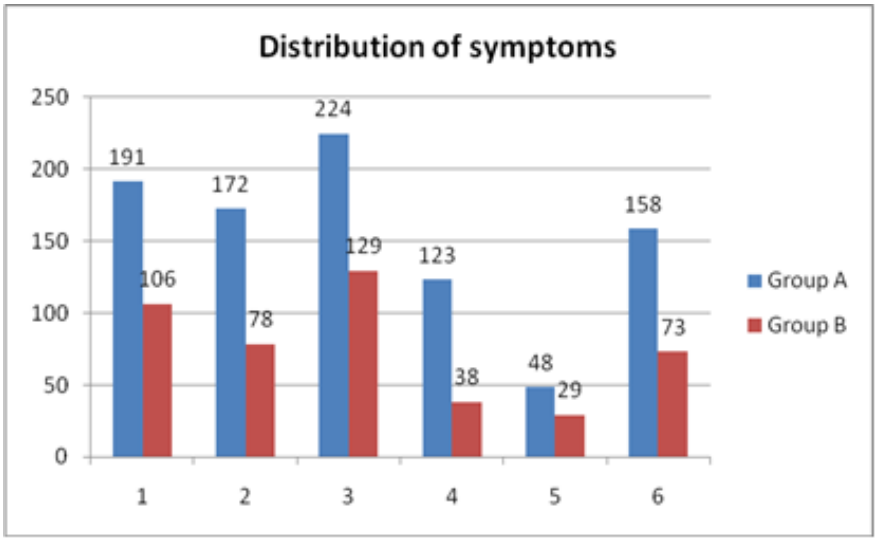


**Figure 1 – Distribution of symptomatic patients. 1.** Chronic pain. **2.** Dysmenorrhea. **3.** Metrorrhagia. **4.** Feeling of fullness. **5.** Urinary incontinence. **6.** Dyspareunia

The treatment in both groups was surgical, this being one of the admission criteria in the study. Out of 28809 patients hospitalized in our obstetrics and gynecology clinic, between 2015-2019, 3173 were diagnosed with uterine fibroids or uterine fibromatosis, the prevalence of the diagnosis over the study time interval, of 5 years, being 11.01%. From the number of 2645 gynecological surgical procedures performed, 1136 were hysterectomies with an average of 227 hysterectomies per year and a percentage of 43% of the total interventions. In our selected groups, of the 480 surgeries, the most common was the total hysterectomy with bilateral adnexectomy:

274 (57%), followed by total interanexial hysterectomy: 44 (9.16%) and subtotal interanexial hysterectomy: 37 (7.7%). Laparoscopic or laparoscopically assisted interventions as well as vaginal hysterectomy were recorded in lower percentages (6%, 2.5% and 2.9%, respectively) and were generally reserved for patients with contraindications to open surgery.

The average duration of the operation was 141 minutes in group A, respectively 125.6 minutes in group B. The average hospitalization time was 6.62 days in group A and 6.31 days in group B. Average volume of blood loss was 219.43 mL in group A and 135 mL in group B, respectively, this being the only notable difference in terms of intraoperative parameters analyzed. Postoperative complications had extremely low and similar rates in both groups of 2.6% and 2.2%, respectively (Table 3).

| Surgical parameters | Group A | Group B |
|---|---|---|
| Average duration of surgery | 141 minutes | 125,6 minutes |
| Average hospitalization time | 6,62 days | 6,31 days |
| Medium volume of blood loss | 219,43 mL | 135 mL |
| Complications rate | 2,6% | 2,2% |

**Table 3 – Surgical parameters**

Analysis of the microscopic appearance of the endometrium showed us interesting differences comparing the two groups. The endometrial hyperplasia and neoplasms were not the subject of our study and that those previously diagnosed were not included in the study, noting here only those that appeared as a surprise of the final histopathological diagnosis. We found an acute inflammatory endometrial appearance in group A in a large percentage, 31.66% of patients, while in patients in group B the appearance was rather chronic (45.55%) and atrophic (11.66%). The frequency of simple and atypical hyperplasia was approximately the same in the two groups. Another important difference emerged from the statistical analysis, namely a much higher incidence of cell atypia and in situ adenocarcinoma in group B, 1.66% compared to 0.33%. The incidence of endometrial neoplasia in group B (2.77%) was more than 8 times higher compared to group A (Table 4).

| Endometrium | Group A | Group B |
|---|---|---|
| Normal aspect | 91 (30,33%) | 35 (19,44%) |
| Inflammatory / hemorrhagic | 95 (31,66%) | 26 (14,44%) |
| Chronic endometritis | 62 (20,66%) | 82 (45,55%) |
| Proliferative/polypoid aspect | 30 (10%) | 2 (1,11%) |
| Atrophic | 22 (7,33%) | 21 (11,66%) |
| Simple hyperplasia | 60 (20%) | 42 (23,33%) |
| Atypical hyperplasia | 12 (4%) | 10 (5,55%) |
| Endometrial polyps | 36 (12%) | 19 (10,55%) |
| AIS / Atypical Polyp | 1 (0,33%) | 3 (1,66%) |
| Endometrial Neoplasm | 1 (0,33%) | 5 (2,77%) |

**Table 4 – Histopathological appearance of the endometrium**

Summarizing the two histopathological categories, chronic and atrophic endometritis, the difference was significant, 28% of patients in group A compared to 57.22% of patients in group B presenting these aspects. A normal appearance of the endometrium was identified in 30.33% of patients in the first group compared to 19.44% in patients in group B with diffuse uterine fibromatosis (Table 4).

Subsequent analysis corroborated these data with a trend of patients in group B, with diffuse uterine fibromatosis, rather towards a primary sterility (10.5% of patients), explained by an endometrium unfavorable to nesting and maintaining a normal pregnancy. Thus, in these

patients, a higher rate of stopped evolving pregnancies was observed compared to patients in group A where the rate of miscarriages was higher (Table 5), these rates being calculated as the ratio to the total pregnancies obtained (births + abortions spontaneous + stopped evolving pregnancies). Patients with recurrent abortion, with more than 3 pregnancies lost through miscarriage were in a higher percentage in group A (5%) than in group B (3.33%). Probably the higher rate of miscarriages in group A was due to the mechanical effects (wall deformation and pressure) exerted by the fibromatous nodules as well as due to the accentuated peristalsis of the uterine muscles. The distribution of fibromatous nodules in group A was: 538 intramural nodules with an average size of 5.62 cm, 188 subserosal and 158 submucosal, here the average size being only 1.05 cm. Completion of the statistical analysis will show the influence of fibroids (number, size and position) in group A on the quality of the endometrium and implicitly on fertility, compared to patients in group B with diffuse uterine fibromatosis, without fibromatous nodules.

| **Fertility** | **Group A** | **Group B** |
|---|---|---|
| Patients with miscarriage | 98 (32,6%) | 25 (13,88%) |
| Number of miscarriages | 144 | 36 |
| Number of patients with recurrent abortion | 15 (5%) | 6 (3,33%) |
| Number of patients with stopped evolving pregnancy | 73 (24,33%) | 38 (21,11%) |
| Number of stopped evolving pregnancies | 76 | 46 |
| Patients with primary sterility | 21 (7%) | 19 (10,5%) |
| Patients with secondary sterility | 44 (14,6%) | 12 (6,65%) |
| Spontaneous abortion rate | 16,74 % | 7,809 % |
| Stopped in evolution pregnancy rate | 8,83% | 9,978 % |
| Total number of pregnancies obtained | 860 | 461 |
| Births | 640 | 379 |

**Table 5 – Fertility parameters**

## Discussions

First, submucosal fibroids have been implicated in infertility or recurrent miscarriage. In 2008, Klatsky and colleagues showed in a systematic review that women with submucosal fibroids had lower implantation rates (3-11.5% vs. 14-30%) and a higher incidence of early pregnancy loss (47% compared to 22%) compared to women without fibroids [4]. A 2013 Cochrane analysis concluded that hysteroscopic myomectomy improves the pregnancy rate from a reference level of 21% to 39% [5]. Regarding the intramiometrial fibroids, the effects they have on the endometrium and fertility are being debated, the studies presenting quite varied results. In addition, there is controversy among specialists in the field regarding the different influence on the endometrium depending on the size of the fibroid [6].

The period of time in which the endometrium becomes receptive to embryo implantation is known as the "window of implantation" (WOI). WOI occurs between 7 and 10 days after the increase of luteinizing hormone, respectively days 21-24 of the normal menstrual cycle and is the time when the endometrium prepares for blastocyst nidation [7]. The necessary steps for the successful implantation of the embryo are: apposition, adhesion and invasion [8]. Critical to these processes are genes in the homeobox family (HOX) that encode proteins that act as important transcription factors in the development of the female embryo and reproductive tract [9]. These genes are also essential for the functional development of the endometrium during the menstrual cycle and for endometrial receptivity. HOX-A10 and HOX-A11 seem to be the most important, both are expressed in the endometrium in the proliferative phase of the menstrual cycle under the influence of progesterone [10]. In addition, both proved to be deficient in the secretory phase in women with low implantation rates [11].

The expression of different cytokines and their receptors on the endometrium and on the

surface of the blastocyst during early pregnancy suggests their roles at different times of implantation [12]. For example, females of opossum mice with a natural mutation in the M-CSF (Macrophage Colony Stimulating Factor) gene have significantly low fertility [13], and mice with a zero mutation in the Lif gene encoding leukemia inhibitor factor (LIF) have had a complete failure of implantation. [14]. Other studies that have used IL-11Rα mutant mice have also shown that IL-11 is crucial for endometrial decidualization but not for attachment reaction [15]. LIF is expressed in endometrial cells but also in stromal cells that surround the blastocyst at the time of the attachment reaction. This suggests that LIF has a dual role: first in preparing the uterus for nesting and later in the adhesion reaction [16]. There are authors who suggest that VEGF is important for uterine vascular permeability and angiogenesis during implantation, its expression but also VEGF receptors increase during pregnancy throughout the uterus in response to steroid hormones [17].

Numerous genes have been analyzed, and the most important are those encoding the synthesis of FGF, IGFs, bone morphogenetic proteins (BMPs), Wnts signaling pathway proteins, Indian hedgehog proteins (IHH) and their specific receptors [18].

Our study analyzed 7 parameters related to fertility (number of births, number of miscarriages, number of stopped evolving pregnancies, premature births, miscarriage rate, stopped evolving pregnancy rate, duration of infertility in years) in relation to the number, size and position of fibroids. Our study also followed statistical correlations between these parameters and the histopathological aspects of the endometrium. Factors involved in both the etiopathogenesis of uterine fibromatosis and in the mechanisms of nidation such as IGF2, FGFb, VEGF are undergoing immunohistochemical analysis. We also analyzed comparatively in the two groups the MMP2 metalloproteinases involved in the nidation mechanisms by degradation of the extracellular matrix and dislocation of the deciduous cells by the syncytiotrophoblast and the final results will be published in a future article.

## Conclusion

Infertility due to uterine fibromatosis is a research topic in all university centers around the world. Clearer and better defined in gynecological practice, over time, are accidents and complications that can occur in a pregnancy obtained on a fibromatous uterus or scarred uterus after myomectomy or myometrectomy. We looked at the impact that uterine fibroids had on the lives of patients included in our study through chronic pain, heavy or persistent bleeding, and influences on fertility and sex life.

Recurrent implantation failure is an important cause of female infertility; therefore, pregnancy rates can be improved by optimizing endometrial quality and receptivity. Uterine fibromatosis influences the histological appearance of the endometrium consequently a better understanding of the mechanisms by which fibromatosis changes the quality of the endometrium and the discovery of treatment methods that will target molecular, paracrine or autocrine factors of these pathological mechanisms will obviously provide a chance in addition to patients to get a normal pregnancy.

Due to the very high incidence of uterine fibromatosis and due to the postponement of a pregnancy, in today's society, until the 3-4 decades of a woman's life, we emphasize the real importance of establishing treatment methods as conservative as possible and identifying clear protocols in uterine fibroid management. In our opinion, this pathology is a real public health problem due to the severe or long-term impact it has on the lives of our patients.

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