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REVIEW PAPER

# Rapidly growing uterine myoma – should we be afraid of it?

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## Abstract

During a year, myomas may undergo radical changes in their dimensions – from decreasing by 90% to growing by 200%. On average, myomas of the uterus increase in volume by 20–30% annually in the premenopausal period. On the other hand, myomas regress spontaneously in about 20% of women. After menopause uterine fibroids stabilize or regress. Every new or growing lesion of the uterus after menopause has to be diagnosed. There is no general definition of fast growing uterine myoma. The presence of fast growing uterine myoma, regardless of its definition, is associated with some clinical issues: it may become symptomatic (pain, bleeding, bulk symptoms), may be responsible for infertility, and a malignant process (leiomyosarcoma) may be present. Regardless of common belief, the risk of sarcoma is not related to the size of the uterus or its fast enlargement. The prevalence of sarcoma in myomas is 0.26%, and in rapidly growing myomas is 0.27%. Treatment should be individualized, selected for the age of the woman and her expectations (preservation of fertility, uterus), symptoms, size and localization of the myomas. The methods of surgical treatment of unsuspected "rapidly growing myomas" are the same as those of common uterine fibroids. Minimally invasive surgery is optimal, but a decision has to be made after evaluation of the risk factors of sarcoma.

**Key words:** sarcoma, fast growing myoma, fast enlargement of uterus.

## Introduction

Uterine myomas (fibroids) are the most common gynecological pathologies. Their prevalence is 70–80% of women about the age of 50. In most cases the myomas are asymptomatic and diagnosed during routine physical or ultrasound examinations. About 20–50% of uterine myomas give clinical symptoms such as: abnormal uterine bleeding, anemia, bulk symptoms, pain, infertility. Symptomatic uterine myomas significantly decrease the quality of life. They have a negative impact on sexual life (43%), work productivity (28%), family and intrapersonal relations (27%) [1].

## Natural history of uterine myomas

### *Premenopausal period*

During a year, myomas may undergo radical changes in their dimensions – from decreasing by 90% to growing by 200%. On average, myomas of the uterus increase in volume by 20–30% annually. On the other hand, myomas regress spontaneously in about 20% of women [2–4].

Mavrelos *et al*. [2] investigated 122 premenopausal women (25–45 years old) with uterine myomas, without hormonal treatment; 61% had multiple myomas. The method of observation was a minimum of 2 ultrasound examinations during a period of 8–90 months (average 21 months between the first and the second USG). Median volume increase of the largest myoma was 35% during the year (range: –7 to 210%). In the case of women before age of 35 the average volume increase of the largest myoma was 70% per year compared to 30% in the case of women over 35 years. In 21% of investigated women a spontaneous regression of myoma was noted. The most dynamic growth was presented by intramural fibroids with a diameter under 2 cm. The growth of fibroids was not linear – periods of fast growth were followed by periods of stabilization or regression [2].

In another study Peddada *et al*. [3] investigated 72 premenopausal women (24–54 years old) with 262 uterine myomas with a diameter range of 1–13 cm (average diameter was 3.2 cm; volume 1.3–1098 $cm^3$) using magnetic resonance imaging (MRI) at the beginning of the study, and then after 3, 6 and 12 months without treatment. The median change of the my-

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omas' volume was 9% in 6 months (high variability: 89–138%). Thirty-four percent of myomas demonstrated fast growth (increase of volume over 20% in 6 months) while 7% of myomas spontaneously regressed (decrease of volume over 20% in 6 months). Different myomas in the same woman grew or shrunk at different speeds. Single myomas were growing faster than multiple myomas [3].

In the next study Baird *et al.* [4] investigated 36 women with total of 101 uterine myomas without treatment. The inclusion criterion was: at least 1 myoma with 5 cm diameter, or uterus size of 12 weeks of pregnancy (volume of 200–250 $cm^3$). They were examined using MRI at the beginning and after 3, 6 and 12 months of the study. The median growth of myoma was 7% in 3 months. Thirty-seven percent of myomas presented periods of accelerated growth (volume enlargement by > 30% in 3 months with changes of size by at least 30% in subsequent MRI examination intervals). One percent of myomas presented periods of regression (shrinkage by > 30% in 3 months with size changes of min. 30% during MRI scans). Each myoma in the same woman had its own speed of volume changes. Among many parameters, only the size of the myoma was associated with periods of increased short-term changes of their volume: high variability under 5 cm of diameter was noted. In the first 3-month intervals of examination 31% of myomas with periods of short-term changes were observed, and in the last 6-month stage it was just 7% [4].

Thus the review of literature revealed that the most dynamic growth usually occurs in the case of small (< 5 cm) myomas. Episodes of intensive increase (> 30% of volume in 3 months) are observed in about 35% of women – in most cases it is only a short-term change (a few months). This increase of size is not constant; after a period of growth, stabilization or regression of the myoma usually occurs. Current clinical practice requires follow-up examinations of women with uterine fibroids every 6 months, because if observed myomas present fast growth (3-month periods); a longer period of observations (at least 6 months) may reveal that it was only a short-term phenomenon [2–4].

### *Postmenopausal period*

After menopause uterine fibroids stabilize or regress. Every new or growing lesion of the uterus has to be diagnosed. The investigations may be delayed in women taking hormonal replacement therapy (HRT) – in these cases the diagnostic workup should be performed in 3–6 months after cessation of HRT.

## Rapidly growing uterine myomas

There is no general definition of fast growing uterine myoma. In the literature most cases are classified and analyzed on the basis of the arbitrary diagnosis of "fast growth of myoma".

Some authors have defined "rapid uterine or myomatous growth" in their studies as: an increase by 6 weeks' gestational size over 1 year [5] or ≥ 20% increase in volume per 6 months [3] or more than 30% increase in volume per 3 months during one interval of observation, with the difference between that growth rate and at least one of the other two interval growth rates of ≥ 30% [4].

The presence of a fast growing uterine myoma is associated with some clinical issues:

- it may become symptomatic – pain, bleeding, bulk symptoms,
- in conceptional age the myoma might be responsible for infertility,
- a malignant process (leiomyosarcoma) might be present.

### *Uterine myomas and the risk of sarcoma*

The spectrum of tumors arising from smooth muscles of the uterus is wide: from begin myomas with a good prognosis (leiomyoma), through tumors with unclear malignant potential (STUMP – smooth uterine muscle of uncertain malignant potential, good prognosis) to leiomyosarcoma.

Parker *et al.* [5] reviewed the records of 1332 patients operated on for presumed leiomyoma and they found the diagnosis of sarcoma in just 3 out of 1332 (0.23%) women, and only 1 of them (0.08%) was leiomyosarcoma. This one case was the only one with sarcoma in a series of 371 women with "rapid growth of the leiomyomas" noted in the history (0.27%) [5]. Rapid uterine growth defined as an increase by 6 weeks' gestational size over 1 year was observed in 198 women – there was no presence of sarcoma and the diagnoses were as follows: in 123 patients (62%) – myomas, in 32 patients (16%) – myomas and adenomyosis, in 23 (12%) – degeneration of myomas, in 12 (6%) – cell fibroids, in 5 (2.5%) – only adenomyosis, in 3 (1.5%) – atypical myomas [5].

A review of 39 studies with 6815 patients operated on for uterine myomas revealed only 18 cases of leiomyosarcoma (0.26%) [5]. The percentage of leiomyosarcoma increased proportionally to the age of the operated women: from about 0.1% in premenopausal women to 1–1.7% in those older than 60 years. In 580 cases of uterine sarcomas only 15 (2.6%) women had a history of fast growing uterus [5].

Thus, the review of the literature showed that, in opposition to common belief, the risk of leiomyosarcoma is not associated with a fast growing myoma or uterus.

### *Differential diagnosis: uterine myoma/sarcoma*

Clinical symptoms, USG, and standard MRI cannot distinguish uterine myoma from sarcoma. Chest X-ray may reveal metastasis in lungs.

Goto *et al*. [6] reported that using a combination of MRI (with intravenous gadolinium) with serum LDH could be reliable in the diagnosis of uterine sarcoma, but the authors stated that it should be confirmed in other studies before wide acceptance. Other authors using different techniques of MRI with gadolinium contrast showed specificity of 95–100% and positive predictive value of 53–100% in diagnosing uterine sarcomas [7, 8]

The closest direct diagnostic approach is endometrial biopsy. Endometrial biopsy is positive in 33–68% cases of uterine sarcoma in general and sensitivity is about 52% (for leiomyosarcoma – 35%) [9–11]. The sensitivity of dilation and curettage or endometrial biopsy is similar [12].

### Factors increasing the risk of sarcoma

- Age 50–70
- Black race (2 times higher risk than in white race)
- Pelvic irradiation in history
- Tamoxifen treatment (5 years or more) in history
- Hereditary myomatosis
- Renal cell carcinoma syndrome
- Retinoblastoma in childhood
- No reaction to pharmacological or conservative treatment [12]

### Asymptomatic myomas

Over a half of uterine myomas are asymptomatic (diagnosed usually during routine gynecological examination). After myoma is diagnosed, the disease should be discussed with the patient, with the recommendation of routine follow-up examinations every 6 months or a doctor's visit in case of symptoms such as abnormal vaginal bleeding, pain, feeling of fullness, increased urge to urinate or to pass stool, etc.

In the case of continuous enlargement of still asymptomatic fibroids the treatment should be started when:
- there is increased risk of malignancy,
- the patient is aware of fertility disorders.

## Treatment

Treatment should be individualized according to the woman's age, expectations (preserving fertility, keeping the uterus), but also symptoms, size and localization of myomas. Treatment could be:
- conservative (pharmacological, interventional),
- surgical.

### Pharmacological treatment

Drugs effective in reducing the size of myomas and abnormal uterine bleeding:
- antagonists of GnRH – relugolix, elagolix,
- agonists of GnRH – buserelin, goserelin, leuprorelin, nafarelin, triptorelin,
- selective modulators of progesterone receptors – ulipristal acetate (UPA), mifepristone.

Drugs effective in reducing abnormal uterine bleeding, but not significantly decreasing myomas size:
- intrauterine device with levonorgestrel,
- oral contraceptives,
- progestins,
- danazol.

### GnRH antagonists

There is an orally used combined drug (relugolix + oestradiol + norethisterone) on the market which causes a significant reduction in fibroid volume (12–17%), menstrual bleeding and pain [13].

#### GnRH agonists

Therapy lasts for 3 or 6 months. There is a reduction of myoma volume up to 50%, but it is temporary and usually there is re-growth of the fibroids within 12 weeks after finishing the treatment.

#### Ulipristal acetate

Because of the cases of severe liver damage, nowadays use of UPA (in Europe) might be considered only for intermittent treatment of moderate and severe symptoms of myomas in premenopausal women, when fibroid embolization or surgical treatment is inappropriate or failed.

### Conservative interventions

#### Uterine artery embolization

This is a method which belongs to the interventional radiologist's range of procedures. It is based on injection of an occlusive drug into one or both uterine arteries, causing hypoxia of the myoma. The result is a reduction of fibroid volume by 33–75% and control of abnormal menstrual bleeding in 83–96% of patients. However, this method is not recommended as a treatment of infertility: compared to surgical myomectomy, the percentage of pregnancies is lower and the percentage of miscarriages is higher after embolization.

Among interventional conservative procedures, uterine artery embolization is the best tested and the most successful therapeutic method for symptomatic myomas in selected women who want to keep their uterus [1].

#### Magnetic resonance-guided focused ultrasound

The magnetic resonance-guided focused ultrasound method can be used in the case of women with symptomatic uterine myomas who want to preserve their

uterus. The reduction in the volume of fibroids obtained is 4–32%. Limitations of this method are: long procedure time, only one fibroid can be treated at a time and high percentage of skin complications (about 7%) [1].

### SURGERY

The methods of surgical treatment of unsuspected "rapidly growing myomas" are the same as common uterine fibroids.

#### Enucleation of myomas

It is a procedure for women who want to preserve their fertility or uterus. The risk of relapse of the fibroids is 15–55%. GnRH agonists may be used to reduce the volume of myoma before surgery. Myomectomy of fibroid not suspected of malignancy should be performed with a minimally invasive method such as hysteroscopy, laparoscopy or minilaparotomy.

#### Hysterectomy (total or supracervical)

Hysterectomy is the most effective treatment method of uterine myomas. It is indicated for women who have ended their reproductive plans and do not want to preserve their uterus. Hysterectomy performed due to uterine myomas without any suspicion of malignancy should be performed with a minimally invasive method such as a laparoscopic or transvaginal approach.

#### Intraoperative assessment of uterine fibroids

During the operation a suspicion of sarcoma is suggested by:

- poorly defined border of lesion,
- soft, homogeneous consistency,
- yellow color of tumor.

If there are multiple myomas in the uterus and a malignant process is suspected, the pathologist should be asked for intraoperative histopathologic examination (frozen section) of the largest lesion (in the case of coexistence of many fibroids, sarcoma is usually found in the largest one). However, negative intraoperative examination cannot exclude a sarcoma.

## Conclusions

In premenopausal women during a year large changes of the volume of myomas (from a decrease of its size by 90%, to enlargement by 200%) may occur. Episodes of accelerated growth were noted in about 35% of women – in most cases it is just a short-term change (3–6 months). Regardless of common belief, the risk of sarcoma is not related to the size of the uterus or its fast enlargement. The prevalence of sarcoma in myomas is 0.26%, and in rapidly growing myomas it is 0.27%. Treatment should be individualized, selected for the age of the woman and her expectations (preservation of fertility, uterus), symptoms, size and localization of the myomas. The decision has to be made after evaluation of the risk factors of sarcoma.

## Disclosure

The authors report no conflict of interest.

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