

# Significance of postmenopausal uterine leiomyomas: Focus on variants

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## Abstract

**Aim:** To investigate the differences in leiomyoma pathophysiology by patient age at the time of surgery and the possible significance of postmenopausal uterine leiomyomas, particularly variants.

**Methods:** We retrospectively reviewed data from 471 patients who underwent surgery for uterine leiomyomas and evaluated their clinical data.

**Results:** Overall, 441 (93.4%) women were premenopausal and 30 (6.4%) were postmenopausal. There were no differences in the frequency of the coexistence of ovarian steroid-dependent diseases among age groups. Common histopathological features were observed in most cases despite menopausal status; however, the incidence of variants among postmenopausal patients was high compared to that among premenopausal women (23.3% [7/30] vs 3.2% [14/441], respectively). Among the variant leiomyomas in postmenopausal patients, lipoleiomyomas comprised six.

**Conclusion:** Although progesterone is known to play a vital role in promoting leiomyoma growth, it reportedly performs dual actions and does not always stimulate leiomyoma growth. Our study may support the idea that the dual action of progesterone is the primary reason for the surgical treatment required for uterine leiomyomas in the postmenopausal period. We also found that lipoleiomyoma might be the most common uterine leiomyoma variant requiring surgical treatment among postmenopausal women. Thus, we must consider the diagnosis of uterine lipoleiomyoma in postmenopausal women with uterine leiomyomas.

**Key words:** menopause/hormone therapy, steroid hormones/hormone receptors/metabolism, uterine leiomyoma/adenomyosis.

## Introduction

Uterine leiomyomas, also called fibroids, are common benign reproductive tract tumors. Despite being generally benign, uterine leiomyomas are responsible for significant morbidity in a large proportion of women.

Uterine leiomyomas tend to appear after menarche, grow during the reproductive years and then stabilize or regress after menopause and affect women in their fourth and fifth decades.<sup>1</sup> However, considerable numbers of postmenopausal patients reportedly undergo surgery for uterine leiomyomas.<sup>2,3</sup> To date, only a few studies have examined leiomyoma growth

over time and determined their significance in the postmenopausal period. For this reason, here we investigated the differences in leiomyoma pathophysiology by patient age at the time of surgery as well as the possible significance of uterine leiomyomas, particularly variants, in the postmenopausal period.

## Methods

We retrospectively reviewed data from women who underwent surgery for uterine leiomyomas between January 2007 and December 2014 at Yokohama

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Municipal Citizen's Hospital, Yokohama, Japan. We evaluated clinical data including surgical indication, parity, body mass index (BMI) and pathological results, including the presence of endometriosis and/or endometrial hyperplasia. The statistical analysis was performed using STA13 (Light Stone) statistical analysis software. To compare intergroup patient characteristics and data, Mann-Whitney *U*- and chi-square tests were used for continuous and categorical variables, respectively. This study was approved by the Yokohama Municipal Citizen's Hospital Institutional Review Board and written informed consent was waived because of the retrospective design.

### Results

A total of 471 patients underwent surgery for uterine leiomyomas at our hospital between January 2007 and December 2014. The highest incidence of leiomyomas was observed in women aged 40–49 years (63.9%), followed by women aged 30–39 (17.4%) and those aged 50–59 years (13.4%). The incidence of leiomyomas in women aged 60 years and above was 3.4% (Table 1). The mean patient age was 40.6 years, while the median age was 45.0 years (range 24–81 years). Pelvic pressure was the primary surgical indication among women aged 20–29, 30–39 and 60 years and above, while hypermenorrhea was the primary indication for women aged 40–49 and 50–59 years. A suspicion of malignancy as the surgical indication was more common among women aged 50–59 or 60 years and above. There were no significant differences in the co-occurrence of endometriosis or endometrial hyperplasia among the age groups.

Among the patients who underwent surgery for leiomyomas, 6.4% (*n* = 30) were postmenopausal, while 93.6% (*n* = 441) were premenopausal (Table 2). Leiomyoma variants were observed in 21 patients: 11 lipoleiomyomas, five cellular leiomyomas, three mitotically active leiomyomas, one intravenous leiomyoma and one metastasizing leiomyoma (Table 2). Therefore, the incidence of variants was 4.5% of the leiomyomas, while lipoleiomyomas comprised 2.3% of the leiomyomas. In common myomas, the incidence of postmenopausal women was low (23/450, 5.1%). On the other hand, in variant type, the incidence of postmenopausal patients was significantly higher than that of common myomas (7/21, 33.3%) (*P* < 0.001) (Tables 2,3). Hypermenorrhea was the most common surgical indication in cases of common

**Table 1** Characteristics of uterine leiomyomas by patient age

Age at the time of surgery	20–29 (n = 9)	30–39 (n = 82)	40–49 (n = 301) reference	50–59 (n = 63)	60+ (n = 16)	Total (n = 471)
Nulliparity, <i>n</i> (%)	8 (88.9)	59 (71.9)	100 (33.2)	13 (20.6)	3 (18.8)	183 (38.9)
Presence of endometriosis, <i>n</i> (%)	0 (0)	11 (13.3)	67 (22.3)	18 (28.6)	3 (18.8)	99 (21.0)
Presence of hyperplasia, <i>n</i> (%)	0 (0)	2 (2.4)	9 (3.0)	3 (4.8)	0 (0)	14 (3.0)
Reason for operation						
Pelvic pressure, <i>n</i> (%)	7 (77.8)	48 (58.5)	122 (40.5)	26 (41.3)	9 (56.3)	212 (45.0)
Hypermenorrhea, <i>n</i> (%)	3 (33.3)	30 (36.6)	185 (51.5)	28 (44.4)	0 (0)	246 (52.2)
Dysmenorrhea, <i>n</i> (%)	0 (0)	13 (15.8)	42 (14.0)	4 (6.3)	0 (0)	59 (12.5)
Suspected malignancy, <i>n</i> (%)	0 (0)	0 (0)	2 (0.66)	4 (6.3)	4 (25.0)	10 (2.1)
Other, <i>n</i> (%)	0 (0)	5 (6.1)	8 (2.7)	9 (14.3)	3 (18.8)	25 (5.3)
BMI (kg/m <sup>2</sup> ), mean ± SD	22.1 ± 1.83	22.2 ± 3.49	22.7 ± 3.44	23.5 ± 4.21	22.0 ± 3.95	22.7 ± 3.58

\**P* < 0.05. BMI, body mass index; SD, standard deviation.

**Table 2** Characteristics of patients who underwent surgical treatment of uterine leiomyomas

Age (years)†	45.0 (24–81)
Body mass index (kg/m <sup>2</sup> )†	21.9 (15.4–42.9)
Before menopause	441 (93.6%)
After menopause	30 (6.4%)
Pathology, <i>n</i> = 471	
Conventional type	450 (95.5%)
Variant type	21 (4.5%)
Lipoleiomyoma	11
Cellular leiomyoma	5
Mitotically active leiomyoma	3
Intravenous leiomyomatosis	1
Metastatic leiomyoma	1

†Values are given as median (range).

myomas, followed by pelvic pressure. In contrast, pelvic pressure was the most common surgical indication in cases of variants. There were no significant intergroup differences in the frequency of the coincidence with endometriosis or endometrial hyperplasia.

The incidence of variants was higher (7/30, 23.3%) in postmenopausal patients than in premenopausal patients (14/441, 3.2%) (Table 4). Six lipoleiomyomas and one cellular leiomyoma were observed among the postmenopausal patients with leiomyoma variants. More than half of the lipoleiomyomas (6/11, 54.5%) were found in the postmenopausal patients (30 women), a figure that was significantly higher than the proportion of premenopausal patients (441 women) with lipoleiomyomas (Table 5). The mean age of patients with lipoleiomyomas tended to be higher than that of those with variants, but statistically not significant. No significant differences were observed in BMI, tumor size, frequency of complication with endometriosis or malignancy in the gynecological field (Table 5).

All except one patient with a leiomyoma variant had several nodules; the other had one nodule. All except one of the nodules of the variant leiomyomas

were the largest tumors. One patient with lipoleiomyoma had a history of treatment for gynecologic malignancy (breast cancer).

## Discussion

Uterine leiomyomas are known to appear after menarche, develop during the reproductive years and stabilize or regress after menopause<sup>1</sup>; ovarian steroids are believed to play a central role in leiomyoma growth.<sup>4</sup> This study revealed that the incidence of surgically treated leiomyomas for women aged 50–59 years was 13.4%, while that for women aged 60 years and above was 3.4%. In a previous report, the highest incidence of surgically removed uterine leiomyomas was observed among women 40–49 years (46.7%), followed by those 50–59 years (35.3%). It was also reported that, although myomas were significantly less common among post- than premenopausal women, the incidence was still almost 10% among women aged 55–59 years and 10.3% among women older than 60 years.<sup>2</sup> Another study analyzed 959 cases of surgically treated uterine myomas and reported that the highest incidence was observed among women aged 41–50 years (62.4%), followed by women aged 51–60 years (18.8%) and those 31–40 years (16.9%). The incidence for women aged 20–30 years was 1.2%, while that for women older than 60 years was 0.7%.<sup>3</sup> These observations indicate that considerable numbers of elderly patients, who should have low levels of ovarian steroid hormones, undergo surgery for uterine leiomyomas.

Progesterone rather than estrogen reportedly plays a vital role in promoting leiomyoma growth.<sup>4</sup> However, most leiomyomas identified early in pregnancy remained the same even reduced in size over the course of pregnancy despite increased circulating

**Table 3** Comparison of characteristics between common and variant uterine leiomyomas

	Common type ( <i>n</i> = 450)	Variant type ( <i>n</i> = 21)	<i>P</i> value
Chief complaint			
Pelvic pressure	203 (45.1%)	9 (42.9%)	0.839
Hypermenorrhea	238 (52.9%)	8 (38.1%)	0.185
Dysmenorrhea	58 (12.9%)	1 (4.8%)	0.271
BMI†	22.7 ± 3.59	23.1 ± 3.31	0.496
Postmenopausal	23.5 (5.1%)	7 (33.3%)	<0.001*
Comorbidity			
Endometriosis	95 (21.1%)	4 (19.0%)	0.821
Endometrial hyperplasia	13 (2.9%)	1 (4.8%)	0.621

\**P* < 0.05. BMI, body mass index.

**Table 4** Characteristics of the uterine leiomyoma variants

No.	Age Parity Pathology		Chief complaint				Mass Enlargement size (cm)	Comorbidity	
	Age at menopause	Pathology	BMI	Abdominal mass	Hypermenorrhea	Dysmenorrhea		Other complaint	Endometriosis
1	43	2					2	No	
2	65	2	23	○	○		10	Yes	○
3	65	2	23	○			8	Yes	
4	54	3	20				7	Yes	Breast
5	41	1	22				10	Yes	○
6	49	2	21		○		4.5	Yes	
7	75	2	23				11	Yes	
8	44	1	25		○		9	Yes	
9	44	0	30	○			30	Yes	
10	65	0	23	○			12	Yes	
11	72	3	27	○			6	Yes	○
12	44	2	23		○		4	Yes	
13	73	2	18				16	Yes	
14	48	1	20	○			10	Yes	
15	45	2	29		○		8	Yes	
16	39	0	20	○		○	9	Yes	
17	47	1	20		○		6	Yes	○
18	41	2	29		○		7	Yes	
19	39	3	24	○			14	Yes	
20	47	2	24	○			30	Yes	
21	42	3	21				10	Yes	○

BMI, body mass index (kg/m<sup>2</sup>).

**Table 5** Comparison of characteristics between lipoleiomyomas and other variants

	Lipoleiomyomas ( <i>n</i> = 11)	Others ( <i>n</i> = 10)	<i>P</i> value
Age (years)†	56.1 (41–75)	46.5 (39–73)	0.083
Post menopausal	6 (54.5%)	1 (10.0%)	0.031*
BMI (kg/m <sup>2</sup> )†	23.4 (19.4–30.4)	22.8 (17.8–29)	0.724
Tumor size (cm)†	10.0 (2.0–30)	11.4 (4.0–30)	0.645
Suspected malignancy	1 (9.1%)	1 (10.0%)	0.943
Combination of endometriosis	2 (18.2%)	2 (20.0%)	0.916
Gynecologic neoplasm	1 (9.1%)	0 (0%)	0.329

\**P* < 0.05. †Mean (range).

concentrations of estrogen and progesterone.<sup>5</sup> The effect of the levonorgestrel-releasing intrauterine system on leiomyoma size reportedly varies remarkably.<sup>6</sup> Finally, leiomyomas are reportedly able to grow at different rates over time and spontaneous regression can occur at any age, not just after menopause.<sup>7</sup> These observations suggest that progesterone may have dual actions on leiomyoma growth, both stimulating and inhibiting it.<sup>4</sup> Therefore, the primary cause of leiomyoma growth after menopause may be this dual action of progesterone.

Microscopic examinations of leiomyomas surgically treated during the postmenopausal period showed common histopathological features in most cases (data not shown). We also previously reported that lipoleiomyomas were the most common uterine variants among postmenopausal women requiring surgery. Lipoleiomyomas primarily occur in the uterine corpus of postmenopausal women.<sup>8</sup> Fifty-eight (82.8%) patients were reportedly postmenopausal in an analysis of 70 consecutive women with 76 lipoleiomyomas.<sup>9</sup> These reports suggest that lipoleiomyomas are relatively common leiomyoma variants among postmenopausal women requiring surgical treatment. The incidence of lipoleiomyomas was 0.35–2.9% of leiomyomas and 0.28–2.1% of patients.<sup>8–12</sup> In the current study, the incidence of lipoleiomyomas among leiomyoma patients was 2.3% (11/471). Therefore, our findings seem consistent with previous results.

Of 76 (75.7%) patients with lipoleiomyomas, 53 had different types associated with hyperestrogenic status such as adenomyosis, endometriosis, endometrial hyperplasia, polyps, complex atypical endometrial hyperplasia and gynecologic carcinomas, suggesting that estrogenic manifestations may be an important factor in lipoleiomyoma development.<sup>9</sup> On the other hand, a case was reported in which the levels of cytosolic estrogen and progesterone receptors were lower in the lipoleiomyoma than in the myometrium; decreased steroid receptors was speculated to be

responsible for the lipomatous neometaplasia in this tumor.<sup>8</sup> It was also reported that the etiology of lipoleiomyomas may be related to the estrogen deficiency that occurs after the menopausal transition.<sup>12</sup> In our study, one patient with lipoleiomyomas had a history of breast cancer (9.1%). In this study, the incidence of endometriosis was 99 of the entire 471-patient cohort (21.0%) and two of the 11 patients with lipoleiomyoma (18.2%). Therefore, it is difficult to speculate on the relationship between lipoleiomyomas and estrogen, and further studies are needed to understand it.

We found that all variant leiomyomas including lipoleiomyomas occurred as single tumors except in one case of two lipoleiomyomas. It was already reported that lipoleiomyomas may rarely be multiple but are often single with size variations.<sup>9</sup> Cases of more than two lipoleiomyomas have not been described in the literature. The reason why uterine lipoleiomyomas are rarely multiple is currently unknown.

In conclusion, uterine leiomyomas can grow or persist after menopause, possibly because of the dual actions of progesterone, and lipoleiomyomas are important variants in the postmenopausal period. The pathophysiology of uterine leiomyomas, including lipoleiomyomas, is not yet fully understood. Further studies are needed to better understand uterine leiomyomas and explore new treatment strategies for them.

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## Disclosure

None declared.

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