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## GYNAECOLOGY

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# Prevalence of Vitamin D Deficiency in Thai Women with Uterine Fibroids

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## ABSTRACT

**Objectives:** To determine the prevalence and associated factors of vitamin D deficiency in Thai women with uterine fibroids.

**Materials and Methods:** A cross-sectional observational study was conducted on 181 Thai women aged 21-49 diagnosed with at least one uterine fibroid with a diameter of 10 mm or greater by ultrasound. The volume of uterine fibroids was calculated using the ellipsoid volume formula. Serum concentrations of 25-hydroxyvitamin D (25(OH)D), parathyroid hormone, and calcium were measured. Then, the participants were stratified into three groups according to their vitamin D status.

**Results:** The prevalence of vitamin D deficiency in Thai women with uterine fibroids was 69.6%. The mean serum concentrations of 25(OH)D, parathyroid hormone, and calcium were  $18.8 \pm 5.8$  ng/ml,  $47.9 \pm 17.8$  pg/ml, and  $9.2 \pm 0.5$  mg/dl, respectively. Neither serum 25(OH)D levels nor serum calcium levels were significantly associated with total uterine fibroid volume (crude mean difference (MD) = -0.01, 95% confidence interval (CI) = -0.02, 0.2,  $p = 0.949$ , crude MD = -0.19, 95%CI = -0.48, 0.1,  $p = 0.193$ , respectively). However, there was a significant association between serum parathyroid hormone (PTH) levels and total uterine fibroid volume (Adjusted MD = -0.02, 95%CI = -0.06, -0.001,  $p = 0.006$ ).

**Conclusion:** Although a high prevalence of vitamin D deficiency was observed among Thai women with uterine fibroids, no significant association was found between low serum 25(OH)D levels and the presence of uterine fibroids.

**Keywords:** Vitamin D deficiency, 25-hydroxyvitamin D, uterine fibroids.

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# ความชุกของภาวะวิตามินดีบกพร่องในหญิงไทยที่เป็นเนื้องอกกล้ามเนื้อมดลูก

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## บทคัดย่อ

**วัตถุประสงค์:** เพื่อศึกษาความชุกและปัจจัยที่เกี่ยวข้องกับภาวะวิตามินดีบกพร่องในหญิงไทยที่เป็นเนื้องอกกล้ามเนื้อมดลูก วัสดุและวิธีการ: การศึกษานี้เป็นการศึกษาเชิงพรรณนาภาคตัดขวางในหญิงไทยจำนวน 181 คน ที่มีอายุ 20-49 ปี ที่มาเข้ารับการรักษาที่โรงพยาบาลราชวิถีตั้งแต่เดือน มิถุนายน 2562 ถึงเดือนมีนาคม 2563 ซึ่งได้รับการวินิจฉัยว่ามีเนื้องอกกล้ามเนื้อมดลูกอย่างน้อยหนึ่งก้อนและมีขนาดมากกว่าหรือเท่ากับ 10 มิลลิเมตรจากการทำอัลตราซาวด์ จากนั้นนำขนาดก้อนเนื้องอกมดลูกมาคำนวณหาปริมาตรโดยใช้สูตรปริมาตรทรงรี และเก็บเลือดตรวจเพื่อหาระดับความเข้มข้นของวิตามินดี (25-hydroxyvitamin D; 25(OH)D), พาราไทรอยด์ฮอร์โมน และแคลเซียม

**ผลการศึกษา:** จากผู้เข้าร่วมงานวิจัยจำนวน 181 คน พบค่าความชุกของภาวะวิตามินดีบกพร่องในหญิงไทยที่เป็นเนื้องอกกล้ามเนื้อมดลูกคิดเป็นร้อยละ 69.6 ค่าเฉลี่ยระดับความเข้มข้นของวิตามินดี (25-hydroxyvitamin), พาราไทรอยด์ฮอร์โมน และแคลเซียม คือ  $18.8 \pm 5.8$  นาโนกรัม/มิลลิลิตร,  $47.9 \pm 17.8$  พิโกกรัม/มิลลิลิตร และ  $9.2 \pm 0.5$  มิลลิกรัม/เดซิลิตร ตามลำดับ โดยไม่พบรความสัมพันธ์อย่างมีนัยสำคัญทางสถิติระหว่างผลการวิทีมของปริมาตรรวมเนื้องอกกล้ามเนื้อมดลูกกับระดับชีรัม 25-hydroxyvitamin D (crude mean difference (MD) = -0.01, 95% confidence interval (CI) = -0.02, 0.2,  $p = 0.949$ ) และระดับชีรัมแคลเซียม (crude MD = -0.19, 95%CI = -0.48, 0.1,  $p = 0.193$ ) อย่างไรก็ตาม พบความความสัมพันธ์อย่างมีนัยสำคัญทางสถิติระหว่างผลการวิทีมของปริมาตรรวมเนื้องอกกล้ามเนื้อมดลูกกับระดับชีรัมพาราไทรอยด์ฮอร์โมน (Adjusted MD = -0.02, 95%CI = -0.06, -0.001,  $p = 0.006$ ).

**สรุป:** แม้ว่าจะพบอัตราภาวะวิตามินดีบกพร่องสูงในหญิงไทยที่มีเนื้องอกกล้ามเนื้อมดลูก แต่ไม่พบรความสัมพันธ์อย่างมีนัยสำคัญระหว่างระดับความเข้มข้นของวิตามินดีในเลือดที่ต่ำกับการมีเนื้องอกกล้ามเนื้อมดลูก

**คำสำคัญ:** เนื้องอกกล้ามเนื้อมดลูก, ภาวะวิตามินดีบกพร่อง, ระดับวิตามินดีในเลือด

## Introduction

Uterine fibroids are monoclonal tumors of smooth muscle cells of the myometrium. It has been recognized that it is the most common benign tumor of the uterus in reproductive women<sup>(1)</sup>. A study found that the incidence of fibroids among African American women by age 35 was 60%, and it was over 80% by age 50<sup>(2)</sup>. Moreover, a previous study revealed that the incidence of uterine fibroids among Asia women was around 20 to 40%<sup>(3)</sup>. Symptoms of uterine fibroids range from asymptomatic to many symptoms that interfere with the quality of life, such as abnormal uterine bleeding, abdominal pain, and compressive symptoms<sup>(2, 3)</sup>. Although the etiology of uterine fibroids is still unclear, molecular biology studies of these tumors suggested a relationship between uterine fibroids and several factors, including hormones, genetics, and growth factors, especially transforming growth factor  $\beta 3$  (TGF  $\beta 3$ )<sup>(2)</sup>. Recently, many studies have noted that vitamin D deficiency was another risk factor for uterine fibroid development<sup>(4-8)</sup>.

Vitamin D is a group of steroid compounds, soluble in fats, which impact several parts of the human body through their receptors, which can be found in various organs, including musculoskeletal, nervous and immune systems, as well as myometrium and uterine fibroid tissue. It has been noted that vitamin D affects cell proliferation and differentiation, inhibiting angiogenesis and stimulating apoptosis<sup>(1)</sup>. Many studies reported that vitamin D has an effect against the growth of uterine fibroids by inhibiting TGF  $\beta 3$ , resulting in a decreased extracellular matrix (ECM) and uterine fibroid volume<sup>(1, 9)</sup>.

Nationwide reports in Thailand revealed that the prevalence of vitamin D deficiency ranged from 9% to 32%<sup>(10-12)</sup>. However, no study identified the prevalence of vitamin D deficiency among Thai women with uterine fibroids. Therefore, this study aimed to evaluate this prevalence and associated

factors of vitamin D deficiency in Thai women diagnosed with uterine fibroids.

## Materials and Methods

### Sample size

This cross-sectional observational study was conducted between June 2019 and March 2020 in both the outpatient and inpatient gynecologic departments of Rajavithi Hospital, Bangkok, Thailand. This study was approved by the Institutional Review Board (IRB) of Rajavithi Hospital, and written informed consent was obtained from participants. The sample size was calculated using an infinite population proportion formula<sup>(13)</sup> based on the previous study by Paffnoni et al<sup>(6)</sup>, which reported the prevalence of vitamin D deficiency in women with uterine fibroid at 63%; alpha values and accepted error were set at 0.05 and 12.5%, respectively. The sample size required was 149 participants. The 20% addition for dropouts was included; therefore, the total number of participants was 179.

### Participants

Women aged 20-49 years diagnosed with at least one uterine fibroid with a diameter of 10 mm or greater confirmed by ultrasound were recruited into this study. Women with one or more of the following conditions were excluded: history of previous myomectomy, chronic systemic disease, malignancy, adenomyosis, pregnancy, lactation, menopausal women, abortion, and pregnancy loss in the past six months, oral contraceptive / hormonal agents utilization in the past three months, history of vitamin D or calcium replacement in the past three months. The clinical characteristics of each patient were recorded. Blood samples of 25-hydroxyvitamin D [25(OH)D], parathyroid hormone (PTH), and calcium were collected and measured on the same day of the ultrasound examination.

## Measurement

Ultrasonography was performed by experienced gynecologist staff using a GE Voluson S8 ultrasound machine fitted with a 2-4 MHz endovaginal probe for the transvaginal scan and a 4-9 MHz convex probe for the abdominal scan. The sonographic appearance of fibroids was defined as symmetrical, well-defined, hypoechoic, and heterogeneous masses.

A fibroid with more than 50% of its diameter bulging out of the uterine contour line was defined as a subserous fibroid. Intramural fibroids were those lining mostly within the uterine shape. Fibroids distorting the uterine cavity were defined as submucosal type. The volume of uterine fibroids was calculated by the ellipsoid volume formula ( $a \times b \times c \times 0.523$ ), where a is height, b is width, and c is depth<sup>(7)</sup>.

## Assay

25(OH)D levels were analyzed using the cobas e602 autoanalyzer (Roche Diagnostics, Thailand) with the electrochemiluminescence immunoassay (ECLIA) technique. The sensitivity of this assay is 3 ng/mL, and the coefficient of variation is less than or equal to 5.94%<sup>(12)</sup>. Serum levels of 25(OH)D were categorized into three different groups according to the Endocrine Society Clinical Practice Guideline recommendations, including vitamin D deficiency (below 20 ng/mL), vitamin D insufficiency (21-29 ng/mL), and vitamin D sufficiency (30-100 ng/mL)<sup>(14)</sup>.

Serum PTH levels were measured by cobas e602 autoanalyzer (Roche Diagnostics, Thailand) with chemiluminescent technique (coefficient of variation is 1.94%). Serum PTH levels between 15-65 pg/ml are defined as a normal range. Additionally, serum calcium levels were analyzed by cobas c702 autoanalyzer (Roche Diagnostics, Thailand) with a

colorimetric assay technique (coefficient of variation is 1.8%), and a normal range is noted between 8.6-10 mg/dl.

## Statistical analysis

Data analysis was performed using Statistical software SPSS version 25 (SPSS Inc, Chicago, IL, USA). As appropriate, descriptive analysis was performed using means  $\pm$  standard deviation (SD), percentage, median, and interquartile range. Categorical data were analyzed using chi-square and Fisher's exact test as appropriate. For continuous data with normal distribution, student t-test and one-way analysis of variance (ANOVA) test were performed, while Mann-Whitney U-test and Kruskal-Wallis test were performed for continuous variables with non-normal distribution. The factors associated with the presence of uterine fibroids were analyzed using univariate and multivariate logistic regression analysis, as well as Pearson correlation. A p value  $< 0.05$  was considered statistically significant.

## Results

A total of 183 Thai women diagnosed with at least one uterine fibroid with a diameter of 10 mm or greater participated in this study. Two women were excluded due to incomplete laboratory results. The baseline characteristics of participants are revealed in Table 1. The age of participants ranged from 21 to 49 years (mean age,  $41.3 \pm 5.7$  years). Also, the mean body mass index (BMI) was  $24.5 \pm 4.8$  kg/m<sup>2</sup>. Regarding uterine fibroids, the diameter of uterine fibroids ranged from 1 cm to 20 cm, and the mean total fibroids volume was 53.8 cm<sup>3</sup>. The most common type of uterine fibroids in our study was intramural fibroids, and dysmenorrhea (35.4%) was the most common symptom, followed by abnormal uterine bleeding (34.8%). Moreover, the mean levels of serum 25(OH)D, calcium, and PTH were  $18.8 \pm 5.8$  ng/ml,  $9.2 \pm 0.5$  mg/dl, and  $47.9 \pm 17.8$  pg/ml, respectively.

**Table 1.** Baseline characteristics of patients with uterine fibroids.

Variables	Total (n = 181)
Age (years), mean (SD)	41.3 (5.7)
BMI (kg/m <sup>2</sup> ), mean (SD)	24.5 (4.8)
Parity, median (min-max)	0 (0-4)
Age at menarche (years), mean (SD)	13.2 (1.5)
Family history of uterine fibroids (%)	28 (15.5)
Education (%)	
Primary school or less	19 (10.5)
Secondary school	40 (22.1)
University or more	122 (67.4)
Working (%)	
Indoor	141 (77.9)
Indoor and outdoor	36 (19.9)
Outdoor	4 (2.2)
Sunscreen using (%)	
No	32 (17.7)
Yes	149 (82.3)
Uterine fibroids	
Amount, median (min-max)	1 (1-9)
Maximal size (cm), median (min-max)	4.9 (1.0-20.0)
Total volume (cm <sup>3</sup> ), median (min-max)	53.8 (0.4-4,190.5)
Type of uterine fibroids (%)	
Submucous	6 (3.3)
Intramural	108 (59.7)
Subserous	28 (15.5)
Mixed	39 (21.5)
Asymptomatic (%)	48 (26.5)
Symptoms (%)	133 (73.5)
Abnormal uterine bleeding*	63 (34.8)
Dysmenorrhea	64 (35.4)
Urinary symptoms	51 (28.2)
Gastrointestinal symptoms	31 (17.1)
Others	7 (3.9)
Laboratory	
Serum vitamin D level (ng/ml), mean (SD)	18.8 (5.8)
Serum calcium level (mg/dl), mean (SD)	9.2 (0.5)
Serum PTH level (pg/ml), mean (SD)	47.9 (17.8)

BMI: body mass index, SD: standard deviation, PTH: parathyroid hormone

\*Abnormal uterine bleeding is defined as bleeding from the uterine corpus that is abnormal in duration, volume, frequency, and/or regularity according to FIGO AUB system 2018<sup>(15)</sup>

The participants were stratified into three groups according to their vitamin D status defined by the Endocrine Society Clinical Practice Guideline recommendations: vitamin D deficiency referred to as serum 25(OH)D level below 20 ng/ml, insufficiency

as 25(OH)D serum level of 21-29 ng/ml, and sufficiency as a 25(OH)D serum of 30-100 ng/ml<sup>(14)</sup>. It was revealed that the prevalence of vitamin D deficiency among Thai women with uterine fibroids was 69.6% (Table 2). No significant differences

regarding age, BMI, family history of uterine fibroids, number, type, and total volume of uterine fibroids were observed among the three groups. Nevertheless, the prevalence of vitamin D deficiency was significantly

higher in women with indoor work ( $p = 0.035$ ) and sunscreen use ( $p = 0.045$ ). The three groups had no significant differences concerning serum calcium and PTH.

**Table 2.** Comparison between factors and serum vitamin D levels.

Variables	Vitamin D deficiency (n = 126)	Vitamin D insufficiency (n = 44)	Vitamin D sufficiency (n = 11)	p value
Age (years), mean (SD)	40.7 (6.1)	42.2 (4.7)	43.9 (3.8)	0.100 <sup>a</sup>
BMI (kg/m <sup>2</sup> ), mean (SD)	24.3 (4.8)	24.6 (4.8)	26.7 (4.5)	0.267 <sup>a</sup>
Parity, median (min-max)	0 (0-4)	0 (0-3)	2 (0-3)	0.133 <sup>b</sup>
Age at menarche (years), mean (SD)	13.2 (1.5)	13.1 (1.7)	12.6 (1.6)	0.314 <sup>a</sup>
Family history of uterine fibroids (%)	21 (16.7)	6 (13.6)	1 (9.1)	0.743 <sup>c</sup>
Working (%)				0.035 <sup>a, c</sup>
Indoor	103 (81.7)	33 (75.0)	5 (45.5)	
Indoor and outdoor	22 (17.5)	9 (20.5)	5 (45.5)	
Outdoor	1 (0.8)	2 (4.5)	1 (9.1)	
Sunscreen using (%)				0.045 <sup>a, c</sup>
No	20 (15.9)	7 (15.9)	5 (45.5)	
Yes	106 (84.1)	37 (84.1)	6 (54.5)	
Uterine fibroids				
Amount, median (min-max)	1 (1-5)	1 (1-6)	1 (1-9)	0.682 <sup>b</sup>
Maximal size (cm), median (min-max)	4.9 (1.0-20.0)	4.4 (1.0-17.0)	5.6 (1.5-7.2)	0.953 <sup>b</sup>
Type (%)				0.745 <sup>c</sup>
Submucous	5 (4)	1 (2.3)	0 (0)	
Intramural	72 (57.1)	30 (68.2)	6 (54.5)	
Subserous	19 (15.1)	6 (13.6)	3 (27.3)	
Mixed	30 (23.8)	7 (15.9)	2 (18.2)	
Symptoms (%)				0.401 <sup>c</sup>
Asymptomatic	35 (27.8)	12 (27.3)	1 (9.1)	
Symptomatic	91 (72.2)	32 (72.7)	10 (90.9)	
Serum calcium (mg/dl), mean (SD)	9.2 (0.56)	9.3 (0.5)	9.23 (0.39)	0.523 <sup>a</sup>
Serum PTH (pg/ml), mean (SD)	49.01 (17.80)	43.9 (18.49)	50.63 (13.93)	0.235 <sup>a</sup>

BMI: body mass index, SD: standard deviation, PTH: parathyroid hormone

\*Significant difference among 3 groups at  $p < 0.05$ , <sup>a</sup> ANOVA test, <sup>b</sup> Kruskal-Wallis test, <sup>c</sup> Chi-square test

From univariate and multivariate logistic regression analysis, there was no association between the uterine fibroids volume and clinical characteristics, including age, BMI, family history of leiomyoma, and symptoms. Also, neither serum 25 (OH)D levels nor serum calcium levels were associated with the uterine

fibroid volume (crude mean difference (MD) = -0.01, 95% confidence interval (CI) = -0.02, 0.2,  $p = 0.949$ , crude MD = -0.19, 95%CI = -0.48, 0.1,  $p = 0.193$ , respectively). Surprisingly, we found a statistically significant association between the uterine fibroids volume and serum PTH levels (Adjusted MD = -0.02,

95%CI = -0.06, -0.001,  $p = 0.006$ ). One unit increase in serum PTH would downsize the volume of uterine fibroids.

Furthermore, correlation analysis revealed that there was no correlation between the logarithm of the total uterine fibroids volume and both serum 25(OH)D levels ( $r = 0.05$ ,  $p = 0.899$ ) and serum calcium levels ( $r = 0.098$ ,  $p = 0.192$ ). However, a statistically significant negative correlation between the logarithm of total uterine fibroids volume and serum PTH levels was observed in our study ( $r = -0.172$ ,  $p = 0.020$ ).

## Discussion

In gynecologic conditions, it has been noted that uterine fibroids are the most common benign tumor of the uterus affecting reproductive women. Although a relationship exists between uterine fibroids and various factors, including genetics, hormones, growth factors, etc., their etiology is still unclear<sup>(2)</sup>. Recently, it has been demonstrated that hypovitaminosis D was correlated with a high prevalence of uterine fibroids, ranging from 63.3% to 100%<sup>(4, 6, 8)</sup>; additionally, some authors reported that serum vitamin D levels are inversely correlated with the severity of uterine fibroids<sup>(6, 7)</sup>. Many previous studies have revealed that vitamin D deficiency was another factor involved in uterine fibroids development as its effect is able to inhibit the growth of uterine fibroids by inhibiting TGF  $\beta$ 3, leading to decreasing the ECM of uterine fibroids<sup>(1, 9)</sup>.

Our study was the first cross-sectional observational study in Thailand, aiming to determine the prevalence and associated factors of vitamin D deficiency in Thai women with uterine fibroids. Our study revealed that the prevalence of vitamin D deficiency among Thai women diagnosed with uterine fibroids was 69.6%, and the mean serum vitamin D level was 18.8 ng/ml, aligned with previous studies. A case-control study of 384 Italian women reported that the mean serum 25(OH)D3 was significantly lower in women having leiomyomas than that of the control group ( $18 \pm 7.7$  ng/ml vs  $20.8 \pm 11.1$  ng/ml, respectively  $p = 0.010$ ). Also, they documented that the prevalence

of vitamin D deficiency in women with uterine leiomyoma was 63.3%<sup>(6)</sup>. Although they found a trend toward a relationship between low vitamin D serum levels and having more than three uterine fibroids ( $p = 0.08$ ), our results did not find a difference between low serum vitamin D levels and the number of uterine fibroids.

Additionally, our study's mean serum 25(OH)D level was congruent with the results obtained by Sabry et al<sup>(7)</sup>. Their cross-sectional observational study was conducted on 154 premenopausal Egyptian women to identify whether low serum vitamin D levels correlate with an increased risk of uterine fibroids. They revealed that lower serum 25(OH)D levels were significantly associated with the occurrence of uterine fibroids ( $p = 0.001$ ); the mean serum 25(OH)D level in their study was  $19.7 \pm 11.8$  ng/ml. However, we did not find a significant association between low levels of serum vitamin D and the occurrence of uterine fibroids. Moreover, they found a statistically significant inverse correlation between serum 25(OH)D levels and total uterine fibroids volume ( $r = -0.31$ ;  $p = 0.02$ ). Unfortunately, our study revealed no correlation between low serum 25(OH)D and total uterine fibroids volume.

In addition, our results followed a similar trend to the previous study by Kaplan et al<sup>(4)</sup>. Their cross-sectional observational study on 124 Turkish women reported that there was no relationship between vitamin D levels and the size, volume, location, and number of uterine fibroids. Nonetheless, they found a significant correlation between vitamin D deficiency and traditional clothing style, low education, and being housewives. It has been recognized that a variety of factors, such as outdoor activities, sunlight exposure, season, clothing, etc, affect vitamin D levels. This present study also found the similar fashion that indoor working and sunscreen utilization were significantly associated with vitamin D deficiency<sup>(5)</sup>.

Besides, it has been documented that obesity and vitamin D status have a complex relationship. Several studies have highlighted the inverse relationship between hypovitaminosis D and

obesity<sup>(16-20)</sup>. The plausible mechanisms have been proposed, including decreased sun exposure, negative feedback from 1,25-dihydroxyvitamin D3, sequestration in adipose tissue, and volumetric dilution<sup>(21)</sup>. Although our study revealed no association between BMI and the occurrence of uterine fibroids, our findings had a similar trend with this inverse relationship. The mean BMI in our study was  $24.5 \pm 4.8 \text{ kg/m}^2$ , which is in the range of overweight according to the Asian-Pacific cutoff points<sup>(22)</sup>. Also, it has been stated that the Asian population has a higher level of body fat percentage than Australian-Caucasians at the same BMI. This may be an explanation for low levels of 25(OH)D in our study; since vitamin D is a fat-soluble vitamin, it might be sequestered in adipose tissue or diluted in volumetric form in our overweight population.

Interestingly, we found a significant negative correlation between serum PTH levels and uterine fibroids volume ( $r = -0.172$ ,  $p = 0.020$ ). One unit increase in serum PTH would reduce the risk of occurrence of uterine fibroid. Our findings were aligned with the study by Ciavattini A et al<sup>(8)</sup>. Their study aimed to determine the effect of vitamin D supplementation in women with hypovitaminosis D and small-burden uterine fibroids. Similarly, they found a negative correlation but failed to obtain a statistical significance between serum PTH and the total volume of fibroids ( $r = -0.02$ ,  $p = 0.76$ ). A previous study reported that parathyroid hormone-related protein (PTHRP) expression in fibroid tissue was higher than in normal myometrium, and their expression may potentially regulate fibroid growth or differentiation through autocrine or paracrine mechanisms<sup>(23)</sup>. Additionally, it has been noted that vitamin D deficiency is associated with an elevation of serum PTH levels; unfortunately, our results did not carry this association. The convincing reason for this finding may stem from unchanged serum calcium levels in our data.

This study had certain limitations. While experienced gynecologic ultrasonologists performed all the ultrasound scans using a standard technique to assess uterine fibroids, subjective variability

remains. Additionally, the lack of serum albumin to correct serum calcium levels was another limitation in this study.

## Conclusion

There was a high prevalence rate of vitamin D deficiency among Thai women with uterine fibroids, albeit no significant association was found between low serum 25(OH)D and uterine fibroids. Further prospective cohort studies are required to explore the causality between leiomyomas and vitamin D deficiency and to shed light on the potential intervention of vitamin D supplementation in uterine fibroids.

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## Potential conflicts of interest

The authors declare no conflicts of interest.

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