

Original Article

Association of Vitamin D with Uterine Fibroid in Women of Reproductive Age

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Abstract

Objectives: To determine the mean change in fibroid size after vitamin D supplementation in Vitamin D deficient women visiting a tertiary care hospital of Lahore.

Methodology: This quasi-experimental trial study was conducted in department of Obstetrics and Gynecology, Sir Ganga Ram hospital, Lahore. from July 2022 to June 2023. A total of 115 premenopausal women between 40 and 45 years of age having fibroids of less than 5 cm by ultrasound were checked for vitamin D levels. The women having vitamin D levels less than 20ng/ml were included. Vitamin D 200,000IU oral supplementation, once weekly was given till the vitamin D level reached 50ng/ml or above or for 12 weeks' duration whichever was earlier. After 12 and 24 weeks all women had an ultrasound and a difference in size and volume of the uterine fibroid was noted. Mean and standard deviation were calculated for numerical variables like Age, duration of symptoms, BMI and size of fibroid (pre, post and change). Post-stratifications, independent 't' test was applied taking $p \leq 0.05$ as statistically significant.

Results: The mean fibroid size at baseline and post-treatment was 34.23 ± 9.66 mm and 27.18 ± 9.39 mm respectively (p -value < 0.0001). Mean change in fibroid size after vitamin D Supplementation in Vitamin D deficient women was 6.79 ± 1.98 mm.

Conclusion: This study concluded that Serum Vitamin D level inversely correlated with size of uterine fibroid and possibly supplementation of vitamin D reduces size of fibroid in vitamin deficient women.

Keywords: Uterine fibroid, Vitamin D deficiency, Vitamin D Supplementation.

Cite this article as: Munir SI, Razzaq S, Sarwar A, Sial A, Ain QU. Association of Vitamin D with Uterine Fibroid in Women of Reproductive Age. J Soc Obstet Gynaecol Pak. 2026;16(1):141-144. DOI. 0.71104/jsogp.v16i2.954

Introduction

Uterine fibroids are benign monoclonal neoplasms originating from uterine smooth muscle cells (myometrium) and fibroblasts.¹ A hallmark of these fibroids is the excessive production of extracellular matrix (ECM).² Their prevalence ranges from 5.4% to 86%, rendering them the most common benign pelvic tumors among women of reproductive age, although 50% of cases are asymptomatic.³ Uterine fibroids are associated with a range of risk factors, which can be categorized as either modifiable or non-modifiable.

Among the non-modifiable risk factors are age, ethnicity, the influence of both endogenous and exogenous hormones, and the age at which menarche occurs. On the other hand, modifiable risk factors include body mass

index (BMI), dietary patterns, the use of supplements, levels of physical activity, and smoking habits.⁴ The most prevalent symptoms experienced by patients are abnormal uterine bleeding (AUB), heavy menstrual bleeding (HMB), pelvic pain, symptoms related to an enlarged uterus, and infertility, all of which significantly affect the quality of life.⁵

In Pakistan, vitamin D deficiency has been reported to be widespread despite the country's subtropical location and sunny climate, particularly among women. According to a recent study, 90% of premenopausal females had serum 25-hydroxyvitamin D (25[OH]D) values < 50 nmol/L (20 ng/mL).⁶ A recent study on Pakistani population has shown that 46.5% of women in reproductive age had uterine fibroids.⁶ A study showed

Authorship Contribution: ^{1,3}Substantial contributions to the conception or design of the work or the acquisition, ¹Final approval of the study to be published, ^{2,4,5}Drafting the work or revising it critically for important intellectual content.

Funding Source: none

Conflict of Interest: none

Received: Oct 25, 2026

Revised: Mar 08, 2026

Accepted: April 28, 2026

that in the vitamin D-supplemented group, uterine size decreased significantly (-7.14 ± 3.86), compared with a negligible reduction in the non-supplemented group (-0.28 ± 1.98). Fibroid size increased in women who did not receive vitamin D supplementation.⁷

Vitamin D inhibits cell proliferation, increases apoptosis, promotes differentiation, and regulates biological processes such as angiogenesis, extracellular matrix synthesis, and immunological response.⁸ The pathophysiology and progression of fibroid uterus may be linked to the decreased expression of the vitamin D receptor (VDR) in leiomyoma tissue when compared to myometrial tissue.⁹ Blauer et al. discovered that vitamin D replacement can slow the growth of fibroids, reducing the need for surgical intervention, which is especially relevant for pre-menopausal women. This was further supported in a study by Corachan et al., which came to the conclusion that vitamin D's modulation of transforming growth factor-beta is important for controlling appropriate cell cycle death and unchecked growth, which in turn limits the proliferation, fibrosis, and size increase frequently observed in fibroids.¹⁰ The aim of this study was to determine the effect of vitamin D supplementation on the fibroid size in patients who have decreased vitamin D levels.

Methodology

This was quasi experimental study done in outpatient department of Sir Ganga Ram Hospital Lahore. Total 115 cases were included in sample size calculated with 95% confidence level, absolute precision 0.07 and taking the mean change in fibroid size after vitamin D supplementation as 7.14 ± 3.86 .¹¹ After ethical approval and informed consent of patients, they were recruited through non probability consecutive sampling. Inclusion criteria include Pre-menopausal women with ages between 40 to 45 years, single fibroid less than 5cm on ultrasound, diagnosed with vitamin D deficiency with levels less than 20 ng/ml. All those women who have had vitamin D supplementation in the last year, women taking regular calcium and vitamin D daily supplementation; pregnant or lactating women, women with autoimmune disorders, endocrinopathies, malignancy or on-going infectious disease, history of prior myomectomy or other intervention for fibroids were excluded from the study.

All the women were given Vitamin D 200,000 IU orally weekly for 12 weeks' duration. Size of the fibroid was measured initially before starting the treatment and then at 12 weeks, along with vitamin D levels. The size of the

uterine fibroids at each follow up is measured in centimetres with the length of the fibroid being used as the dimension of measurement. Women whose vitamin D level on follow up reaches up to 50ng/ml were given maintenance therapy of 1000 IU oral vitamin D weekly till the end of the study to avoid intoxication. Mean and standard deviation were calculated for numerical variables like Age, duration of symptoms, BMI and size of fibroid (pre, post and change). Frequency and percentages were calculated for type of fibroid. Data was stratified for age, BMI, duration and type of fibroid to address effect modifiers. Post-stratifications, independent 't' test was applied taking $p \leq 0.05$ as statistically significant.

Results

Age range in this study was from 40 to 45 years with mean age of 42.74 ± 1.61 years. Majority of the females i.e. 66 (57.39%) were between 43 to 45 years of age as shown in Table I. Results of this study showed the mean fibroid size at baseline and post-treatment was 34.23 ± 9.66 mm and 27.18 ± 9.39 mm respectively (p -value <0.0001). Mean change in fibroid size after vitamin D Supplementation in Vitamin D deficient women was 6.79 ± 1.98 mm as shown in Table II.

Table I: Demographic Data. (n=115)

	N	%	Mean±SD
Age			42.74 ± 1.61 years
40-42 years	49	42.61	
43-45 years	66	57.39	
Duration of fibroids			8.08 ± 3.08
≤ 9 months	83	72.17	
>9 months	32	27.83	
BMI kg/m²			25.30 ± 4.48
≤ 27	79	68.70	
>27	36	31.30	
Type of fibroid			
Intramural	77	66.96	
Subserosal	38	33.04	
Parity			3.05 ± 1.44
0	2	1.7	
1-2	41	35.7	
3-4	56	48.7	
> 5	16	13.9	

Results have shown that Mean fibroid size decreased from 34.23 mm to 27.44 mm, with a mean reduction of 6.79 mm. This reduction in fibroid size was observed across all parity groups. The highest mean reduction was seen in women with parity ≥ 5 (7.31 mm), though differences between parity groups appear statistically non significant. (Table III)

Table II: Mean change in fibroid size after vitamin D Supplementation.

	Fibroid size		P-value
	Mean	SD	
Pre-treatment	34.23	9.66	0.0001
Post-treatment	27.18	9.39	
Change	6.79	1.98	

Table III: Stratification of change in fibroid size.

Age	Change in fibroid size		P value
	Mean	SD	
40-42 years	7.08	1.86	0.074
43-45 years	6.41	2.10	
Duration of fibroids			0.019
≤ 9 months	7.06	2.01	
>9 months	6.09	1.75	
BMI kg/m²			0.003
≤ 27	6.49	1.87	
>27	7.78	2.06	
Type of fibroid			0.615
Intramural	6.86	1.88	
Subserosal	6.66	2.21	
Parity group			0.294
0	6.50	2.21	
1-2	6.56	1.91	
3-4	6.82	2.09	
≥5	7.31	1.85	

Discussion

Uterine fibroids are the most prevalent benign gynecological tumors among women of reproductive age, and their management is continually advancing with a growing focus on minimally invasive and medical approaches. In recent years, vitamin D has gained attention as a potential therapeutic adjunct due to its involvement in cellular proliferation, apoptosis, and extracellular matrix regulation.

A meta-analysis of randomized controlled trials revealed that vitamin D supplementation is significantly associated with a reduction in fibroid size compared to placebo, with more pronounced effects observed when the treatment duration exceeds eight weeks.¹¹ A study indicated that biweekly administration of 25,000 IU cholecalciferol over a six-month period not only resulted in a reduction of fibroid dimensions but also led to decreased vascularity. This suggests a potential influence on tumor biology that extends beyond mere stabilization of size.¹²

Another study demonstrated that higher baseline serum 25-hydroxyvitamin D levels were associated with reduced fibroid growth, increased rates of fibroid regression, and a decreased incidence of new fibroid development, suggesting a dose–response (biological gradient) relationship between vitamin D sufficiency and favourable fibroid outcomes.¹³ Collectively, these

findings support the hypothesis that vitamin D plays a modulatory role in fibroid pathophysiology.

The findings of the present study are consistent with this evidence, as a statistically significant reduction in fibroid size was observed following vitamin D supplementation. The mean fibroid size decreased from 34.23 ± 9.66 mm at baseline to 27.18 ± 9.39 mm post-treatment, representing a significant reduction ($p < 0.0001$). This suggests that correction of vitamin D deficiency may contribute not only to inhibition of fibroid growth but also to measurable regression in fibroid size.

Similar results were reported in a randomized clinical trial in which vitamin D supplementation (50,000 IU weekly for 8 weeks) resulted in a slight decrease in fibroid diameter (from approximately 43 mm to 42.6 mm) in the intervention group, whereas the control group demonstrated a significant increase in fibroid size (from approximately 42 mm to 47.8 mm). The difference between the two groups was statistically significant ($p < 0.001$). These findings indicate that even short-term vitamin D supplementation may halt fibroid progression, while longer duration or greater correction of deficiency, as seen in the present study, may lead to more pronounced fibroid regression.¹⁴

Another study also found a correlation between lower vitamin D levels and greater fibroid size and growth thus supporting these findings. Serum vitamin D levels in the case and control groups were, 15.26 ± 4.96 ng/mL and 22.45 ± 6.93 ng/mL respectively, which were statistically significant (P value < 0.001).¹⁵ Importantly, the present study also demonstrated that the beneficial effects of vitamin D supplementation were observed across all age groups and irrespective of fibroid location. However, a more pronounced response was seen in patients with a fibroid duration of less than 9 months, indicating that earlier-stage fibroids may be more responsive to vitamin D therapy. Also the Parity does not impact the efficacy of vitamin D treatment as beneficial results are evident in all patients, however it is more efficacious in multipara. (Table III)

According to a recent study, vitamin D supplementation significantly reduces the elastic strain ratio of uterine fibroids and the mean diameter of fibroid size ($P = 0.043$ and $P = 0.038$, respectively). However, there was no discernible change in the blood flow of uterine fibroids ($P = 0.272$). This study has also demonstrated that taking vitamin D supplements significantly reduces heavy menstrual bleeding, dysmenorrhea, and frequent urination.¹⁶ Overall, the findings of the present study, in

conjunction with existing literature, support a biological gradient between vitamin D sufficiency and favorable fibroid outcomes, and suggest that early correction of vitamin D deficiency may play a role in slowing fibroid growth or inducing regression.

Despite these positive findings, the extent of size reduction is small, and vitamin D cannot yet be regarded a standalone therapy. Most studies found that supplementation resulted in fibroid stability or minor volume decreases rather than significant shrinking. The clinical importance of such changes is unclear, particularly in terms of symptom relief, reproductive outcomes, and long-term recurrence rates.

Furthermore, changes in baseline vitamin D status appear to have a substantial impact on outcomes, with larger advantages shown in women who are deficient or insufficient at the start of treatment. Safety factors must also be addressed: while vitamin D supplementation is normally safe, excessive dose increases the risk of hypercalcemia and nephrolithiasis. Therefore, supplementation should be personalized, best guided by baseline serum 25-hydroxyvitamin D levels.

Conclusion

Vitamin D supplementation is associated with a statistically significant reduction in uterine fibroid size, supporting the growing evidence of an inverse relationship between vitamin D status and fibroid growth. Correction of vitamin D deficiency may contribute to inhibition of fibroid progression and possible regression, particularly in early-stage disease. Given its low cost, favorable safety profile, and ease of administration, vitamin D supplementation may represent a useful adjunct in the conservative management of uterine fibroids, especially in women with documented deficiency.

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