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STUDY OF ASSOCIATION OF VITAMIN D LEVEL WITH LEIOMYOMA OF UTERUS

Gynaecology

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KEYWORDS

INTRODUCTION -

Uterine leiomyoma (fibroid) represents a localized proliferation of smooth muscle cells surrounded by a pseudocapsule of compressed muscle fibers. It is the most common benign tumor in the female genital tract and their prevalence during a women's lifetime ranges from 50-80 %. Symptomatic women typically suffer from menstrual disorders, heavy menstrual bleeding, anaemia, pelvic pain and "bulky symptoms" (bladder or rectal pressure). Moreover, uterine fibroids seem to be related to infertility, early pregnancy loss, and several adverse obstetric outcomes. The choice of the appropriate therapy for uterine fibroids is influenced by several factors, including the severity of symptoms, infertility, the tumor characteristics , the patient's age, wish to preserve the uterus, and the desire of future pregnancies.$_2$ The mainstay treatment of uterine fibroid is surgery, in the form of myomectomy or hysterectomy, which in addition to cost burden also preclude future fertility. Therefore, it is crucial to search for novel nonsurgical alternatives for the prevention & management of uterine fibroids. The present study was undertaken to see the association of Vitamin D levels in women with development of leiomyoma and thereby use of vitamin D or its analogue can be a safe, future long term means of reducing the occurrence of leiomyoma in the general population.

MATERIAL AND METHODS-

The study was conducted in the department of obsterics and gynecology at SMS medical college and hospital Jaipur, after ethical clearance from the institutional ethical committee.
Study Type = Hospital base comparative study
Study Design = Cross sectional study
Study Place = SMS medical college, Jaipur.
Study Duration = From February 2019 to February 2020.
Study Universe = All women attending gynaecology OPD in SMS Medical College

Inclusion Criteria

1. Case group comprising of 60 Women between 18-50 years of age who was diagnosed with leiomyoma with mean diameter of >10 mm at ultrasound.
2. Control group comprising of 60 women between 18-50 years whose USG was normal and there was no leiomyoma.
3. Women who were willing to give consent for study.

Exclusion Criteria:

1. Pregnant, lactating and menopausal women
2. Women currently using or who had used a vitamin supplement or any hormonal treatment within the 6 months prior to enrollment
3. Women having malignancy, multiple sclerosis and autoimmune disorders.
4. Severly ill patient
5. Non cooperative

STUDY METHODOLOGY -

After applying inclusion and exclusion criteria informed written consent was taken and women with complain of abnormal uterine bleeding and willing to participate was recruited from dept of obs and gynae SMS medical college Jaipur. Approval from institutional research, review board and ethical committee was taken. Standardized data collection on a predesigned study performa including a full AUB workup after the initial visit was done. Case group comprising of 60 women belonging to age group 18-50 years who was diagnosed with leiomyoma with mean diameter >10mm at ultrasound. Control group comprising of 60 women belonging to age group 18-50 years whose pelvic USG was normal and there was no fibroid. A Brief history was taken and gynaecological examination was done and blood samples was collected for estimation of vitamin D3 level. Ultrasound evaluation was performed on all consenting subjects. Statistical analysis was done using suitable test of significance. Data thus collected was entered in excel sheet to prepare master chart and was subjected to statistical analysis.

Statistical Analysis

Descriptive analysis was measured using means, frequencies, standard deviations, and percentages. The independent t-test was used to compare serum Vitamin D levels across groups. Association of vitamin D level with presence of leiomyoma was assced by using unpaired t test. A P-value <0.05 was considered significant.

RESULTS –

The mean age of 60 cases enrolled in the study was 45.17+/-3.52 years while mean age of controls was 44.98+/- 3.34 years (p value-0.77). The median parity of our cases and controls was 2 and hence there was no difference in the parity of both groups. Family history of fibroids was positive in 21.7% of cases and 6 % of controls (p value-0.08). The mean BMI in cases was 25.22 +/- 4.57 and control was 25.27+/- 3.92(p value-0.95). There was no statistical difference between the incidence of confounding high risk factor of age ,parity, age at menarche, family history of fibroids And BMI in cases and controls. In 60 cases of leiomyoma and in 60 controls the values of serum vitamin D were estimated. The mean level of vitamin D in cases was 17.618 +/- 8.34 ng/ml and control was 46.81 +/- 19.66. The levels of vitamin D were significantly less in cases than in controls. (p value < 0.001). Thus there was statistically significance difference in cases and control.

Table 1: Descriptive Statistics

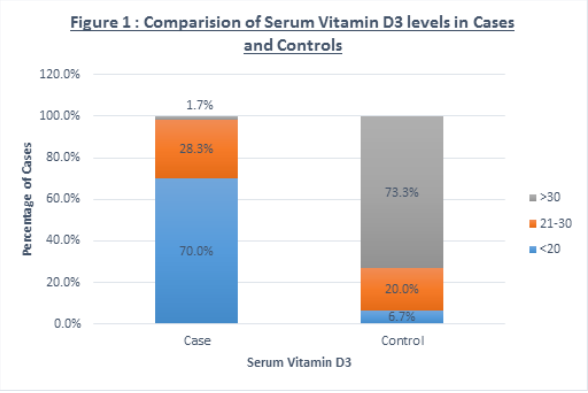
Group		N	Mean	Std. Deviation	Std. Error Mean	t	Df	P Value
Age	Case	60	45.17	3.528	.455	.292	118	.770
	Control	60	44.98	3.337	.431			
BMI	Case	60	25.223340	4.5790354	.5911509	-.061	118	.951
	Control	60	25.271114	3.9295325	.5073005			
S. Vit D3 level	Case	60	17.618	8.3497	1.0779	-10.585	118	.001
	Control	60	46.812	19.6645	2.5387			

Mean age in case group is 45.17±3.528 years and control group is 44.98±3.33 years, there is no statistically significant difference in the mean age between the groups (P=0.77), mean BMI in case group is 25.22±4.57 Kg/m2 and control group is 25.27±3.92 Kg/m2, there is no statistically significant difference in the mean BMI between the groups (P=0.951), mean Serum Vitamin D3 level in case group is 17.62±8.35 and control group is 46.81±19.66, there is a statistically significant difference in.

Table 2: Distribution Of Cases According To Serum Vitamin D3 Levels

S. VitD3 (ng/ml)		Group		Total
		Case	Control	
<20	No of Cases	42	4	46

	Percentage	70.0%	6.7%	38.3%
21-30	No of Cases	17	12	29
	Percentage	28.3%	20.0%	24.2%
>30	No of Cases	1	44	45
	Percentage	1.7%	73.3%	37.5%
Total	No of Cases	60	60	120
	Percentage	100.0%	100.0%	100.0%
2=73.342				P<0.001



The mean Serum Vitamin D3 levels between the groups (P=0.951). on using the WHO criterion , out of our 60 cases 42 (70%) were vitamin D deficient .(p value < 0.001).statistically significant.

DISCUSSION -

vitamin D has emereged to be an important regulator of uterine leiomyoma development. The mean value of vitamin D level in cases was 17.618 +/- 8.34 and control was 46.81+/-19.66 ng/ml with p value < 0.001. Thus, it was statistically significantly lower in cases than in controls. Hence it was observed in our study that vitamin D deficiency was more common in case group and it was statistically significant. Thus vitamin D deficiency is a risk factor for leiomyoma.

Among 60 cases and controls, 42(70%) cases and only 6.7% controls have serum Vitamin D3 levels <20ng/ml, 28.3% of cases and 20% controls have Serum Vitamin D3 levels 21-30ng/ml and 1.7% of cases and 73.3% controls have Serum Vitamin D3 levels >30ng/ml.

The findings of this study showed that the median plasma vitamin D in women with uterine fibroids was significantly lower than in those without fibroids, this is consistent with similar studies done by **Sabry et al.,[3], Baird et al.[4], and Paffoni et al.[5]**. Probably because TGF -ß3 upregulates the synthesis of many of the extracellular matrix (ECM) protein involved in fibrosis55 with resultant extracellular matrix protein over production in human leiomyomas by stimulating the expression of collagen type 1, fibronectin, laminin and proteoglycans as found in uterine fibroids. **Sabry et al.,[3]** found a mean value of vitamin D to be significantly lower in women with uterine fibroids 19.7ng/ml which is higher than the findings of this study and also lower in BLACKS than WHITE subjects (14.2ng/ml vs 25.5ng/ml). **Paffoni et al[5]** found a slightly higher level of vitamin D in women with uterine fibroids 18.0ng/ml, while in women without uterine fibroids the median plasma vitamin D level was found to be 52.1ng/ml which is higher than what **Sabry et al[3]** and **Paffoni et al[5]** found in women without uterine fibroids 22.3ng/ml and 20.8ng/ml respectively. Comparison of both median plasma vitamin D level of women with uterine fibroids 13.5ng/ml IQR 3.8-22.1ng/ml with women without uterine fibroids 52.1ng/ml IQR 30.6-75.0ng/ml, p value = < 0.001 demonstrates inversely correlation between low level of vitamin D with presence of uterine fibroids showing statistically significant negative correlation. Similar findings were shown by **Sabry et al[3]** and **Paffoni et al[5]** in comparing Vitamin D levels in women with or without uterine fibroids (14.2ng/ml vs 22.3ng/ml p=0.001) (18.0ng/ml vs20.8ng/ml) respectively. Furthermore, the study illustrates lowest level of plasma 25 (OH) vitamin D in women with largest fibroid volume dropping to as low as <10ng/ml with large fibroid volume. This could probably be due to the diverse functions of vitamin D mediated predominantly through a G1/S (gap1/synthesis) phase block of the cell cycle and its inhibitory role in cell growth, proliferation related genes (proliferating cell nuclear antigen (PCNA), Cell proliferation markers cyclin D1 (Ccnd1) and proto oncogene Myc which have been reported to be over expressed in leiomyoma compared to normal myometrium. Hence a lower level of vitamin will invariably lead to increased fibroid size. Furthermore is the similar result achieved in the recent in vivo data from Eker rat model showing protective effect of treatment with 1, 25 dihyroxyvitamin D3 shrinkage of uterine leiomyoma tumour. **Sharan et al.[6]and Halder et al.[7]** both demonstrated that 1,25 hydroxyvitamin D3 inhibits proliferation of human uterine leiomyoma cells respectively all exploring the association between Vitamin D and uterine fibroids.

The method used for measurement / analysis of 25(OH) D for this study is the High-Performance Liquid Chromatography (HPLC) and conducted by an experienced and well-trained laboratory scientist. The value of 25(OH)D used to determine insufficient level is < 20ng/ml which is the value considered to be minimum concentration in 2007 workshop consensus report27.

A major strength of the study is the study design, screening with use of ultrasound in women with fibroids, inclusion of women with similar gynaecologic complaints at the gynaecology clinic, and matching for age, parity and BMI in women, within the same study period and participating center may have protected results from other cofounders. These studies were in agreement with our results that vitamin D deficiency is a common finding in patients with fibroids and vitamin D deficiency has emerged as one of the main risk factor.

CONCLUSION-

The study shows that plasma vitamin D levels are significantly lower in women with fibroids. Results showed negative correlation with the size of Fibroid and Vitamin D. Vit D deficiency is a possible risk factor for the occurrence of Uterine Fibroids, so encouraging dietary intake or supplementation may forestall the development of uterine fibroids even in those with genetic predisposition. Decreased levels of Vitamin D may be related to their developing fibroids.

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