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Obstetrics

Estimation of Serum Vitamin D Level and Its Association with the Risk of Epithelial Ovarian Cancer

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Abstract: Ovarian cancer is a disease whose etiology is thought to be due to incessant ovulation and hormonal imbalance and is the most common cancer in women with a lifetime risk of 1 in 100 women. Among various types of ovarian malignancy, epithelial ovarian cancer is reported to be the most common histological type. The objective of the study is to estimate serum vitamin D levels and evaluate association of vitamin D levels with the risk of epithelial ovarian cancer. This prospective case control study was done over a period of 2 years (October 2015 to October 2017) in a tertiary care private teaching hospital. Hundred women were included in our study, of which fifty were epithelial ovarian cancer women with the age group between 20 to 80 years and fifty healthy women as control. 2ml blood sample was drawn in plain vacutainer to measure the serum vitamin D levels and were estimated by Electro-Chemi Luminescence Immuno Assay (ECLIA). Serum vitamin D levels were significantly lower in ovarian cancer women compared to controls ($p < 0.001$). We conclude that Vitamin D level can be a biomarker which was found to be significantly lower in ovarian cancer group.
Keywords: Epithelial ovarian cancer, Vitamin D.

INTRODUCTION

In the female genital tract, ovarian tumours constitute 30% of all cancers [1]. Lifetime risk of women having ovarian cancer is 1 to 1.5% and death due to ovarian cancer is approximately 0.5% [2]. It is the second most common gynecological cancer accounting for 18.8% of all gynecological cancers in developing countries and 28.7% in the developed countries [3].

According to the latest molecular studies, delayed presentation of ovarian cancer and difficulties in its management is attributed to the anatomical site of the ovary and the complexity in its histology [4]. 70% of patients present in advanced stage of the disease with cure rate of less than 40% [5]. The reason for high mortality rate is due to ineffective screening methods which have low sensitivity and specificity.

Vitamin D is a fat-soluble secosteroid hormone. It plays a role in calcium and phosphate metabolism. In the presence of ultraviolet light, vitamin D synthesis is initiated by photoconversion of 7-dehydrocholesterol to pre-vitamin D3 in the epidermis [6]. This is followed by the conversion of pre-vitamin D3 to vitamin D3 in the skin [7] which is further metabolized to 25-hydroxyvitamin D3 in the liver [8,9] and to 1α,25-dihydroxyvitamin D3 primarily in the kidney (1,25(OH)2D3) [10,11] which is the active form of vitamin D.

Based on the concept that low vitamin D levels have a role in the initiation and progression of ovarian cancer, recent studies have proved that ovaries are a target organ for the action of 1,25(OH)2D3 by demonstrating the presence of 1,25(OH)2D3 in ovaries of rat and hen by Immunohistochemistry [12] and ligand binding assays respectively [13]. Study by Johnson *et al*. has reported a decrease in cell number by vitamin D3, therefore giving the first concrete evidence of this correlation [12]. Hence, the present study was planned to estimate the serum vitamin D level and to evaluate the relationship of serum Vitamin D levels in epithelial ovarian cancer.

MATERIALS AND METHODS

This study was conducted in the Department of Obstetrics and Gynaecology & the Department of Oncology at K .S. Hegde Charitable Hospital, Deralakatte, Mangalore. Written informed consent was obtained from all the participants and ethical clearance was obtained from the institutional Ethics Committee of

Nitte University. This case control study was conducted over a period of two years (October 2015 – October 2017).

Study participants

100 samples were included in this study, of which fifty diagnosed epithelial ovarian cancer and fifty controls are matched with cases with respect to age, menopausal status and month of blood drawn. Patients who are not willing to participate in the study, cases of non-epithelial ovarian cancer, known case of chromosomal abnormalities and Vitamin D disorders like hyperparathyroidism, hypoparathyroidism were excluded. For control samples, healthy women with no comorbidities, no malignancies and with the willingness were considered. The detailed clinical history like menopausal status, history of oral contraceptive usage, history of tubal ligation and family history of each patient was recorded.

Sample collection and Measurement of Vitamin D level

2ml of Blood sample was collected in plain vacutainer for serum 25-(OH) vitamin D from all cases and control subjects by venepuncture. The sample was centrifuged and serum was separated. 200ul of serum was used for serum vitamin D level estimation by Vitamin D total Elecsys and Cobas e analyzers kit (Roche) by Electro-chemiluminescence immunoassay (ECLIA).

Vitamin D status is most reliably assessed by measuring Serum 25(OH)D which has been proven to be an accurate marker. Vitamin D level below 20ng/mL (50nmol/L) is defined as Deficiency, vitamin D level ranging from 20 to 29.9ng/mL (52-72nmol/L) is defined as Insufficiency and the Vitamin D level above 30ng/mL defined as Sufficiency by the Journal of Clinical Endocrinology & Metabolism [14].

STATISTICAL ANALYSIS

The collected informations were summarized by using the descriptive statistics such as frequency, percentage, mean and standard deviation, median and interquartile range. Independent sample t-test and the Mann-Whitney U test were used to compare the outcome measures between two groups. The p-value <0.05 was considered as significant. The data management and analysis was performed using Microsoft Excel & SPSS version 21 (SPSS Inc, Chicago, IL, USA).

RESULTS

The age, menopausal status, parity, history of breast, colorectal & genital cancer in family and tubal ligation among cases and controls are shown in the below table. All parameters were not statistically significant except the history of tubal ligation which was statistically significant with a p-value of 0.008.

Table-1: Characteristics of subjects in the study group

Characteristics	Cases (n=50)	Control (n=50)	p- value
Mean age in years	48.26	47.92	
Menopausal status			0.83
Pre-menopausal	30	30	
Postmenopausal	20	20	
Family history of breast, colorectal and ovarian cancer	Nil	Nil	0.153
Parity			
Nulliparous	7	2	
1	6	5	
2-3	28	32	
>4	9	11	
Tubal ligation	10	27	0.008

Vitamin D analysis revealed the median value of serum vitamin D levels in cases were 16 ng/ml whereas in controls was 20.62 ng/ml which was significantly higher with p- value <0.001. Interquartile range in cases was between 11.225 and 19.85 ng/ml whereas in controls it was between 18.45 and 25.15 ng/ml.

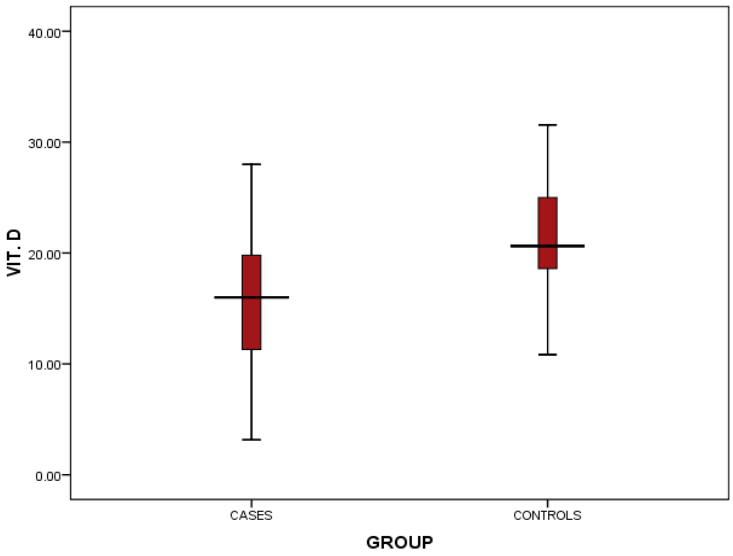

Fig-1: Box plot representing vitamin D levels in cases and controls

Table-2: Serum Vitamin D levels in Cases and Controls

	N	Mean	95% Confidence Interval for Mean	p- value
Cases	50	15.3846	13.6393 - 17.1299	<0.001
Controls	50	21.7972	20.2014 - 23.3930	
Total	100	18.5909	17.2650 - 19.9168	

Serum Vitamin D levels are divided into three groups like Top tertile: Serum Vitamin D >21 ng/ml, Medium tertile: Serum Vitamin D 11-20 ng/ml and Bottom tertile: Serum Vitamin D <10 ng/ml in our study for analysis. Women with lower vitamin D levels (bottom 33%) were at higher risk for epithelial cancer than those with high levels (top 33%) which is statistically significant.

Table-3: Number of Cases and Controls according to tertile levels of serum Vitamin D

Mean of Serum vitamin D level (ng/ml)	Cases (n=50)	Controls (n=50)	p- value
Top tertile (>21)	10(20%)	25(50%)	<0.001
Bottom tertile (<10)	11(22%)	2(4%)	

In reproductive age group vitamin D levels are lower in cases compared to controls which is statistically significant (p-value <0.001) whereas in post-menopausal age group serum vitamin D levels were lower compared to controls though not statistically significant.

Table-4: Mean serum vitamin D (in ng/ml) in reproductive and postmenopausal age group in cases and controls

Mean serum vitamin D in ng/ml			
	Cases	Controls	p- value
Reproductive age group	15.33	22.88	<0.001
Post-menopausal age group	15.83	20.31	0.016

DISCUSSION

Vitamin D is known to be involved in bone metabolism but its role in other diseases like cancer, autoimmune disease and diabetes mellitus are under study. Role of vitamin D in cancer prevention has been widely described in many studies and that the vitamin D deficiency prevalence is high in tropical country like India [15-17]. The reason for this would be the lifestyle of people where most of the women stay indoors, poor intake of dairy products due to social factors and dietary habits [18, 19].

As 85% of the ovarian cancer cases are sporadic and 15% are familial, it has been hypothesized that both genetic and environmental factors may be involved in the development of ovarian cancer [20]. Factors including age, gravidity, tubal ligation, number of ovulatory cycles and family history of ovarian cancer influence the ovarian cancer risk, eventually lifestyle factors like diet, physical activity and exposure to carcinogenic chemicals have an impact [21]. In our study we observed tubal ligation as the protective factor against ovarian cancer.

Earlier studies have shown an inverse relationship between vitamin D levels in blood and incidence of much cancer [22, 23]. In this study we observed lower vitamin D levels in ovarian cancer group. A meta-analysis of randomized controlled trials demonstrated that intake of vitamin D supplements was associated with a significant 7% reduction in mortality from any causes [24]. A serum 25- hydroxyvitamin D3 (25OHD3) concentration of 25nmol/L was associated with a 17% reduction in incidence of cancer, 29% reduction in total cancer mortality, and a 45% reduction in digestive system cancer mortality [25].

In our study, mean of serum vitamin D level in cases is (15.38ng/mL) lower than control group (21.8ng/mL) which is statistically significant. On subset analysis, the participants in the highest tertile had a significant lower risk of ovarian cancer than those in the lowest tertile. The mean vitamin D level of ovarian cancer (15.33ng/mL) was significantly lower than that of controls (22.88ng/mL) in the reproductive age group. Earlier studies conducted by Mohapatra *et al*. Shafie *et al*. had shown the similar results [26, 27].

CONCLUSION

Vitamin D level was found to be significantly lower in ovarian cancer group as compared to control group. Our data reveals that women who had undergone tubal ligation had reduced incidence of ovarian cancer as compared to women who did not undergo tubal ligation and is found to be statistically significant. Analysis of data had revealed that serum vitamin D levels <17 ng/ml have more risk of ovarian cancer compared to levels >17ng/ml. This study helps us to predict that vitamin D supplementation might prevent ovarian cancer though large randomized controlled trial is required to predict the same.

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