Association of Vitamin-D Status and Peripartum Cardiomyopathy - A Hospital-Based Study from South India

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ABSTRACT

BACKGROUND

Recently, the role of vitamin-D on structure and function of cardiomyocytes and associated diseases has been explored very well. The association of vitamin-D in peripartum cardiomyopathy (PPCM) patients is not studied anywhere yet. So, the present study was designed to assess vitamin-D levels in PPCM patients and evaluate its association with clinical severity, echocardiographic parameters, and clinical outcomes.

METHODS

An observational, case-control, hospital-based study conducted at a tertiary care center in India. The study included 30 patients who were diagnosed with PPCM in one group and 60 healthy women who were in the peripartum period in the control group. All the patients underwent physical examinations, blood analysis, and M-mode echocardiographic assessment. An electrochemiluminescence immune assay technique was used to measure the level of vitamin-D.

RESULTS

The mean age of patients in PPCM group was 24.60 ± 3.52 years and in control group was 22.97 ± 2.39 years. The mean vitamin-D levels were 13.61 ± 4.59 ng/ml and 18.87 ± 4.10 ng/ml in PPCM and control groups, respectively ($P < 0.0001$). Left ventricular ejection fraction was 39.73 ± 4.73 % in PPCM group and was 64.47 ± 3.36 % in control group ($P < 0.0001$). A positive correlation was observed between vitamin-D level and left ventricular ejection fraction. However, an inverse correlation was observed between left ventricular dimensions and vitamin-D level.

CONCLUSIONS

Patients with PPCM had lower vitamin-D levels than control group and its deficiency had a significant correlation with cardiac function and clinical severity. However, long-term studies are warranted to know the exact role of vitamin-D in relation of PPCM.

KEYWORDS

Cardiac Function, Cardiovascular Disease, Peripartum Cardiomyopathy, Pregnancy, Vitamin-D Deficiency

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BACKGROUND

Peripartum cardiomyopathy, a diagnostic exclusion, is defined as an idiopathic cardiomyopathy (generally non-ischemic) presenting with heart failure secondary to left ventricular dysfunction (ejection fraction < 45 %) in the last month of pregnancy or within 5 postpartum months without any other evident causes of heart failure.[1,2] It has been found that African and African-American women are at a higher risk of developing PPCM compared to Asian women. In addition to ethnicity, multiparity, multigestational pregnancy, older/younger maternal age, hypertension, diabetes, pre-eclampsia and family history of cardiomyopathy are considered as predisposing risk factors of PPCM. In recent time, few studies have stated that nutritional deficiency in pregnant women can also lead to the development of PPMC.[1,3]

Vitamin-D, commonly known as "bone vitamin", is one of the vital nutrients that play very crucial role not only in maintaining bone health but also in almost all physiologies of the whole body. In the last decade, several newer discoveries have disclosed multiple roles of vitamin-D on the cardiovascular system, cancer as well as on the immune system. The role of vitamin-D on structure and function of cardiomyocytes and associated diseases has been explored well in recent time.[4,5] Furthermore, the deficiency of vitamin-D is frequently observed in pregnant women mainly due to decreased intake of foods containing vitamin-D and skin protection from sunlight. Though the role of vitamin-D in the occurrence of cardiomyopathy has been established in few studies, its role in PPCM is still not known or studied anywhere.

Thus, the present study was designed to evaluate the role of vitamin-D on the occurrence of peripartum cardiomyopathy in pregnant women.

METHODS

This was an observational, case-control, hospital-based study conducted at a tertiary care center in India from March 2018 to January 2020. The study patients were divided into two groups: i) the PPCM group - 30 patients who were diagnosed with peripartum cardiomyopathy, and ii) the control group - 60 healthy women who were in the peripartum period. The study was approved by institutional ethics review board and the written informed consent was received either from patient or patient's family member. The PPCM was strictly diagnosed based on the criteria described in Table 1.[6]

1.	Development of cardiac failure in the last month of pregnancy or within five months of delivery
2.	Absence of an identifiable cause of cardiac failure
3.	Absence of recognizable heart disease prior to the last month of pregnancy
4.	Left ventricular systolic dysfunction demonstrated by echocardiographic criteria such as depressed left ventricular ejection fraction (LVEF < 45 %)

Table 1. Diagnostic Criteria for Peripartum Cardiomyopathy

The patients concurrently suffering from ischemic dysfunctions, endocrine/metabolic disturbances, viral myocarditis, autoimmune diseases (systemic lupus erythematosus, scleroderma, dermatomyositis), severe anaemia (haemoglobin < 7 gm %), and taking chemotherapy drugs and alcohol were excluded from the study.

Measurement Tools and Procedure

All the patients underwent physical examinations, blood analysis and M-mode echocardiographic assessment. Echocardiography measured left ventricular end diastolic diameter, left ventricular end systolic diameter, left atrial size and left ventricular ejection fraction by averaging values from three consecutive cardiac cycles.

Furthermore, vitamin-D levels were measured at the time of diagnosis using Cobas Roche 6000 (C501 + E601) chemistry analyser using electro-chemiluminescence immune assay technique which measures the serum concentrations of 25 (OH) D in the range of 4 – 100 ng/ml. The reference values of endocrine society clinical practice guidelines[7] were used to define vitamin-D level in all the patients (Sufficient: 30 - 100 ng/ml; Insufficient: 20 - 29 ng/ml; Deficient < 20 ng/ml).

Statistical Analysis

All the data were analysed using statistical package for social science (SPSS) version 25.0 (IBM SPSS, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables as frequency with percentage. Independent student's t - test and chi - square test / Fischer's exact test were used in estimating statistical differences among continuous and categorical variables, respectively, with a 95 % level of significance.

RESULTS

The study included 30 patients (mean age: 24.60 ± 3.52 years) with peripartum cardiomyopathy in PPCM group and 60 healthy patients (mean age: 22.97 ± 2.39 years) in peripartum period in control group. The mean gestational age of patients in PPCM and control group was 36.30 ± 2.40 weeks and 37.00 ± 0.00 weeks, respectively. In PPCM group, New York Heart Association class - III dyspnoea was diagnosed in 20 (66.6 %) patients and class - IV dyspnoea in 10 (33.4 %) patients. The baseline characteristics of patients in both the groups is outlined in Table 2.

All the patients in both groups were suffering from anaemia, but none of them had hypertension, type - 2 diabetes mellitus, or hyperlipidaemia. Among patients in PPCM group, only two (6.7 %) were diagnosed with congestive cardiac failure. Supraventricular tachycardia, atrial fibrillation/flutter, valvular heart disease, and transient ischemic attack were not reported in any of the study patient. In PPCM group, 28 (93.3 %) patients had mild to severe pulmonary hypertension, all 30 patients had mild to severe mitral regurgitation and only two (6.7 %) patients had gestational diabetes mellitus.

None of the patient reported multiple gestations, pregnancy-induced hypertension, premature rupture of

membranes, or HELLP syndrome in the peripartum period. Among all 30 cases of PPCM, 26 (86.7 %) patients were diagnosed with cardiomyopathy in antenatal period and 4 (13.3 %) patients were diagnosed with PPCM postnatal. The systolic and diastolic blood pressure in PPCM group were 107.47 ± 29.01 mmHg and 72.67 ± 17.68 mmHg and in control group 111.53 ± 7.79 mmHg and 74.07± 4.73 mmHg, respectively. The pulse rate, respiratory rate and SpO_2 in PPCM and control group were 122.27 ± 9.45 vs 74.07 ± 4.73 mmHg (P < 0.0001), 28.07 ± 6.59 rate/min vs 19.77 ± 1.87 rate/min (P < 0.0001) and 94.8 ± 4.2 % vs 98 % (P < 0.0001), respectively.

Characteristics		PPCM Group (N = 30)	Control Group (N = 60)	P - Value
Age, years (mean ± SD)		24.60 ± 3.52	22.97 ± 2.39	0.01
BMI, kg/m^2 (mean ± SD)		22.03 ± 1.76	20.79 ± 4.23	0.13
Gravidity, n (%)	G1	14 (46.7 %)	28 (46.7 %)	1.000
	G2 and G3	16 (53.3 %)	30 (53.3 %)	
Gestational age at diagnosis, weeks (mean ± SD)		36.30 ± 2.40	37.00 ± 0.00	0.73
Type of delivery	Normal	8 (26.7 %)	46 (76.7 %)	< 0.0001
	Assisted	22 (73.3 %)	14 (23.3 %)	

Table 2. Baseline Demography and Obstetric Parameters

Parameters		PPCM Group	Control Group
Congestive cardiac failure, n (%)	Yes	02 (6.7 %)	00
	No	28 (93.3 %)	
Dyspnoea, n (%)	NYHA Class - III	20 (66.6 %)	00
	NYHA Class - IV	10 (33.4 %)	00
Pulmonary hypertension Severity, n (%)	Mild	12 (40 %)	00
	Moderate	14 (46.6 %)	00
	Severe	2 (6.7 %)	00
	None	2 (6.7 %)	60 (100 %)
Mitral regurgitation severity, n (%)	Mild	20 (66.7 %)	00
	Moderate	6 (20 %)	00
	Severe	4 (13.3 %)	00
	No	0	60 (100 %)
Timing of cardiomyopathy, n (%)	Antenatal	26 (86.7 %)	00
	Postnatal	4 (13.3 %)	00
	Duration of symptoms, weeks (mean ± SD)	6.67 ± 3.59	--

Table 3. Clinical Presentation of all the Patients in Both Groups

BMI: body mass index; NYHA: New York Heart Association

2D echocardiographic examination revealed statistically significant difference between PPCM and control group for left ventricular end-diastolic diameter (54.4 ± 7.90 mm vs 46.1 ± 2.57 mm, P < 0.0001) and end-systolic diameter (42.47 ± 8.56 mm vs 29.93 ± 1.60 mm, P < 0.0001), ejection fraction (39.73 ± 4.73 % vs 64.47 ± 3.36 %, P < 0.0001), and left atrial size (34.93 ± 2.69 mm vs 32.27 ± 3.58 mm, P = 0.001). In PPCM group, Grade - I diastolic dysfunction was found in 10 (33.3 %) patients and Grade - III in 4 (13.3 %) patients. Acute kidney injury (AKI) was observed as a concurrent complication in eight (26.7 %) patients with PPCM. But none of them underwent dialysis and all of them recovered from AKI during the course of hospitalization suggesting pre-renal failure as the cause. In PPCM group, 10 (33.3 %) foetus were pre-term, 2 (6.7 %) had intrauterine growth restriction and 2 (6.7 %) patients underwent intra-uterine device implantation.

All 30 patients in PPCM group received blood transfusion, however, only 2 patients received blood transfusion in control group. During hospital-stay for PPMC, 14 (46.7 %) patients were in intensive care unit (ICU) and 16 (53.3 %) patients were on non-invasive ventilation.

In PPMC group, inotropes were given in 10 (33.3 %) patients, diuretics and beta-blockers were given in all 30 (100 %) patients, angiotensin converting enzyme-I to 6 (20 %) patients, nitrates in 2 (6.7 %) patients. The complications and foetal outcomes to all the patients in both the groups are outlined in Table 4.

	Characteristic	PPCM Group (N = 30)	Control Group (N = 60)
Complication n (%)	Acute kidney injury	8 (26.7 %)	00
Foetal Outcome, n (%)	Normal	16 (53.3 %)	60 (100 %)
	Pre - term	10 (33.3 %)	00
	Intrauterine growth restriction	2 (6.7 %)	00
	IUD	2 (6.7 %)	00

Table 4. Complications and Foetal Outcomes to all the Patients in Both Groups

ICU: intensive care unit; ACE - I: angiotensin - converting enzyme inhibitor; IUD: intra - uterine device

The mean vitamin-D levels in PPCM and control group were 13.61 ± 4.59 ng/ml and 18.87 ± 4.10 ng/ml (P < 0.0001), respectively. Among all, 86.7 % patients in PPCM group and 60 % patients in control group had deficiency of Vitamin-D during peripartum period and no patient in both the groups had sufficient levels of Vitamin-D (Table 5).

	Characteristic	PPCM Group (N = 30)	Control Group (N = 60)	P – Value
Vitamin - D Status	Vitamin - D level (ng/ml)	13.61 ± 4.59	18.87 ± 4.10	< 0.0001
	Insufficient (21 - 29 ng/ml)	4 (13.3 %)	24 (40 %)	0.015
	Deficiency (< 20 ng/ml)	26 (86.7 %)	36 (60 %)	

Table 5. Status of Vitamin-D in Both Groups

2D - Echo Parameters	Correlation Coefficient (r)	P - Value
LVDd	−0.126	0.41
LVDs	−0.291	0.05
LVEF	0.526	< 0.0001
LA size	−0.174	0.254

Table 6. Correlations with Vitamin-D Levels with 2D - Echo Parameters

LVDd: left ventricular diastolic diameter; LVDs: left ventricular systolic diameter; LVEF: left ventricular ejection fraction; and LA: left atrial

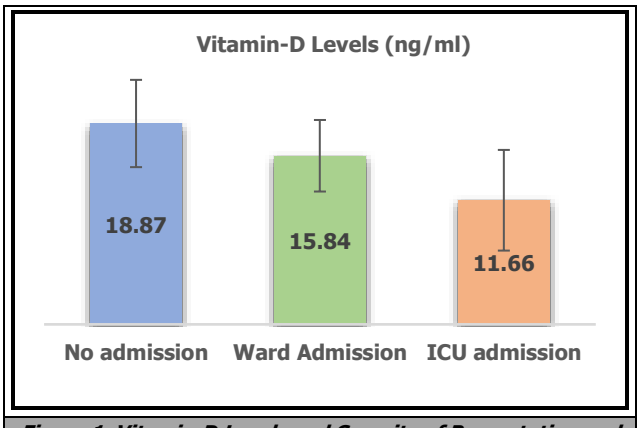

Figure 1. Vitamin-D Levels and Severity of Presentation and Treatment in Patients with Peripartum Cardiomyopathy

Furthermore, it was found that women who were admitted to ICU, normal ward and not admitted had vitamin-D levels of 11.66 ± 4.73 ng/ml, 15.84 ± 3.36 ng/ml and 18.87 ± 4.10 ng/ml (P < 0.0001), respectively (Figure 1). On correlation of vitamin-D level with various echo parameters, a positive correlation was established between

vitamin-D level and left ventricular ejection fraction. On the contrary, vitamin-D level and left ventricular end systolic diameter and left ventricular diastolic diameter represented negative correlation (Table 6).

DISCUSSION

Vitamin D, also functions as a lipid-soluble steroid hormone, is a widely studied vitamin in last decade due to its multiple role in functioning of different vital organ systems of the human body. Despite of this, almost half of the world population is having deficiency of vitamin-D. Although vitamin-D is known for its role in calcium homeostasis and bone metabolism, association of low levels of vitamin-D and increased risk of cardiovascular diseases have been well-established by numerous studies.[5,8-12] The Framingham offspring heart study stated that individuals with vitamin-D level < 15 ng/ml had a 60 % higher risk of development of any major cardiovascular disease.[13] Furthermore, pregnancy and lactation period both are highly associated with a risk of vitamin-D deficiency.[8] Although vitamin-D deficiency has been linked as a cause cardiomyopathy by various studies, the association between vitamin-D deficiency and PPCM has not been reported anywhere in literature yet. Thus, in the present study association of vitamin-D levels and PPCM was studied and significant results were reported which set a stage for similar larger studies.

Vitamin-D either act directly or indirectly on the cardiovascular system. The direct effects of vitamin-D include anti-hypertrophic effects on cardiomyocytes, inhibition of the renin-angiotensin system, maintenance of the myocardial extracellular matrix turnover, affects the cardiac contractility and intracellular calcium handling, regulation of myosin expression and heart energy metabolism. Vitamin-D also protects vessel walls from inflammatory damage by increasing anti-inflammatory cytokines, and by decreasing pro-inflammatory molecules. On the other hand, indirect effects include anti-hypertensive, anti-atherosclerotic, anti-diabetic and anti-autoimmunological properties which ultimately prevent myocardial damage.[5,8,9,12]

The PPCM is a form of cardiomyopathy which advances in a pregnant woman before or in few months after the delivery. The exact pathophysiology of PPCM is not known and considered as multi-factorial[1,2] Some of the studies in literature have suggested that abnormal immune activity and elevated levels of various inflammatory mediators (tumour necrosis factor - á, C - reactive protein, interleukin - 6 and FAS / Apo - 1) may play a role in the pathogenesis of PPCM.[1, 14]

Furthermore, hypocalcaemia is also considered as one of the causes of any form of cardiomyopathy. These few factors of pathogenesis of PPCM can be correlated with the effects of vitamin-D deficiency, as its deficiency leads to increase in inflammatory responses and hypocalcaemia[12,15] Literature also state that low maternal vitamin-D levels has an indirect co-relation with the development of dilated cardiomyopathy, heart failure and other serious cardiac dysfunction in new born child.[16,17]

The present study reported significantly low levels of vitamin-D in patients with PPCM compared to control group (P = 0.015) despite of vitamin-D deficiency (< 20 ng/ml) in both the groups. The left ventricular ejection fraction was significantly low in PPCM group compared to control group (39.73 ± 4.73 % vs 64.47 ± 3.36 %). In this study, a positive correlation was observed between vitamin-D levels and left ventricular ejection fraction (r = 0.526 ; P < 0.0001) and a negative correlation was observed between vitamin-D levels and left ventricular diastolic and systolic diameters (r = 0.126 ; P = 0.41 and r = − 0.291 ; P = 0.05, respectively). These observations were similar with the results of Ameri et al.[18] who studied association of vitamin-D levels in patients with heart failure; S. Priya et al.[19] and V. Polat et al.[20] who studied the correlation of vitamin-D levels in patients with dilated cardiomyopathy.

Hypertension, pre-eclampsia, and respiratory infection have strong association with PPCM, however in our study none of the patient of PPCM were reported to have such disorders. Furthermore, literature stated that most of the women were diagnosed with PPCM after delivery,[1,21] however our study reported 86.7 % cases of PPCM in antenatal stage probably because of high index of clinical suspicion and liberal screening echocardiographic imaging protocol we follow at our institution. The present study showed that lower the levels of vitamin-D, more severe the clinical presentation and more the need of intensive critical care required to PPCM patients. However, vitamin-D deficiency did not show any significant impact on mortality in PPCM.

CONCLUSIONS

From the results of this study, it can be stated that screening and prompt maintenance of sufficient vitamin-D levels in every pregnant woman should be considered in order to avoid development of PPCM and other cardiovascular complications. All physician should be aware of PPCM and its symptoms for early diagnosis and treatment to avoid serious life-threatening complications to mother and even to foetus. Supplementation of vitamin-D in pregnancy might prevent or at least decrease the severity of clinical presentation in PPCM.

However, further studies are required to confirm the possible causal association between vitamin-D levels and PPCM and also to establish the effectiveness of vitamin-D supplements on the prognosis of PPCM patients.

Study Limitations

Small sample size and study design (non-randomized and observational study) were some of the limitations of this study. Another limitation is lack of follow-up details which could have given clear picture of mortality and prognosis of PPCM. Furthermore, the results of our study are not sufficient to prove a causal relationship between vitamin-D deficiency and PPCM, however it set a stage for more accurate and larger studies in future.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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