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Effectiveness of vitamin D supplementation in the early gestational period on lactational mastitis development: A new framework in the risk assessment

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Abstract

Background: Vitamin D (VD) deficiency is known to play a role in many infectious diseases with its immunomodulator effect. We aimed to determine whether optimal VD replacement for women who are deficient in VD, starting from early pregnancy was significantly protective against lactational mastitis (LM).

Methods: This retrospective study was conducted with 132 lactating women applied to general surgery outpatient clinic of a university hospital between February 2021 and May 2021 and divided into two groups as those who used VD supplementation (Group 2) starting from the early gestational period and those who did not receive this supplementation (Group 1). The primary outcome was the effect of treatment of maternal VD deficiency or insufficiency on LM, an inflammatory condition of breast during lactational period ranging from a mild to severe forms. The demographic, birth and breastfeeding-related data including nipple crack and occurrence of LM and laboratory parameters concerning VD metabolism were analyzed and compared between the groups.

Results: The rates of nipple crack, mastitis attack, recurrent mastitis attack and abscess drainage were statistically significantly higher in Group 1 ($p < 0.05$). Further analysis revealed that increased VD use and higher VD levels during lactation (25 ng/ml) decreased the incidence of mastitis attacks by 1.2 and 1.9 times, respectively.

Conclusions: VD deficiency was found to be a noticeable risk factor for the development of LM. Concerted efforts with randomized controlled trials are necessary to further analyze this manageable risk factor, especially by promoting a well-designed and schematized replacement treatment based on VD levels starting from early pregnancy.

Introduction

Breastfeeding is a natural and effective method for infant feeding that has restored its reputation against formula feeding in the last four decades through a growing number of breastfeeding campaigns implemented by various non-governmental healthcare organizations in the form of social responsibility projects across the world [1, 2]. Despite the ongoing aggressive marketing of breastmilk substitutes, the prevalence of exclusive breastfeeding has increased by 50% compared to the 1980s [3]. However, with a given global incidence of 10-33% of breastfeeding women suffer from clinical lactational mastitis (LM) that may be either self-limited or need seeking medical advice and treatment, a puerperal acute inflammatory process of the breasts, especially within the first six months of delivery, and this condition can cause early weaning, resulting in the potential loss of health benefits of breast milk for the infant [4, 5]. Although, the etiology of LM remains controversial with possible multifactorial inflammatory and infectious mechanisms based on bacterial imbalance, it is known that the process starts with milk stasis triggered by the effect of cytokines and causes the emergence of the classical triad of mastitis consisting of pain, redness, and fever [5]. A growing body of evidence has demonstrated that if left untreated or treated inappropriately, the process can progress from the mild form of breast engorgement to the infectious state, and possibly leading to the formation of breast abscesses, which is further frustrating for the patient [4-6]. Although it is unclear by which route the infectious agent reaches the lactiferous

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ducts, potential risk factors for infectious LM have been reported as a history of mastitis attacks, cracked nipples, nipple cream application, use of milk pump, and peripartum antibiotic use7. Staphylococcus aureus is the most frequently isolated pathogenic microorganism in infectious mastitis, while Streptococcus strains (Streptococcus mitis and Streptococcus salivarius) and rarely Corynebacterium spp. also play a role in the etiopathogenesis [8]. Since the earliest and preventable stage of LM is milk stasis, it has been recommended to avoid infrequent and missed breastfeeding, ensure an effective and coordinated suckling of the baby by strengthening mother-baby bonding, encouraging the discharge of milk from the breast, and preventing damage to the nipples as alternative preventive methods; however, none has yet been proven to be effective in preventing the occurrence of LM [5, 9]. To date, the most reliable method is to interrupt the milk-stasis/breast infection pathway to activate mechanisms that protect skin integrity and further preventative approaches might be helpful to strengthen the maternal immune system by supplying natural immunomodulators showing promising results in mouse models including curcumin, alpinetin and chlorogenic acid [10, 11].

Vitamin D (VD) or calciferol, previously known as a fat-soluble steroid, is an essential hormone involved in bone metabolism only through calcium and phosphorus homeostasis. However, in recent years, the investigation of whether VD functions as a physiological regulator of normal immune has provided a new perspective on the non-classical effects of VD. There is a growing body of clinical and laboratory evidence that VD has immunomodulatory, anti-inflammatory and antifibrotic properties and plays an important role in the regulation of cell proliferation, differentiation, and apoptosis [12]. VD from sunlight and diet is metabolized in the liver to 25-hydroxyvitamin D, which is used to determine the patient's VD status. Unfortunately, VD deficiency has gained a pandemic character, with about a third of the world's population not being exposed to sufficient sunlight.13 VD deficiency is known to play a role in the development of many chronic diseases, including common cancers, autoimmune diseases, and cardiovascular diseases [14]. Considering the underregulatory effects of VD deficiency on host immunity, the incidence and severity of many infectious diseases seem to be affected by fluctuations in the VD levels of the affected individual [13-15]. Moreover, different studies have shown an association between VD deficiency and tuberculosis, HIV, respiratory, HCV, diabetic foot and methicillin-resistant S. aureus infections [16-20]. The real matter of debate is whether VD deficiency is only a simple bystander of various infectious diseases or a particularly aggravating contributory factor in the pathogenesis of infections through the downregulation of the innate and adaptive immune response [13, 15].

Given that both inflammation and infection significantly contribute to the etiopathogenesis of LM and considering the documented importance of VD in maintaining a healthy immune system, we aimed to determine whether optimal VD levels achieved by VD replacement during pregnancy were significantly protective against the development of LM.

Methods

Study design

The participants of this retrospective study were recruited at the general surgery outpatient clinics of Medipol University Faculty of Medicine between February 2021 and May 2021. A total of 132 lactating women aged 18 to 45 years who were in the sixth and 12th months of lactation were divided into two demographically similar groups as those who used VD supplementation (n = 83) and those who did not receive this treatment (n = 49), starting from the early gestational period (sixth to 10th weeks of gestation).

The inclusion criteria of the study were being followed up and giving birth at the same university hospital, attending the breastfeeding education program organized at the hospital, and performing exclusive breastfeeding for at least six months, which is the lower limit recommended by the World Health Organization. The exclusion criteria were a history of diseases requiring maternal immunosuppressive treatment, cancer and non-lactational mastitis, and separation of the mother and infant for more than 24 hours during the breastfeeding period. Individuals who had been detected with normal VD levels at the early gestational period, but supplemented with VD during their follow-up due to decline in the VD values were also excluded from the study. The primary outcome was the effect of treatment of maternal VD deficiency or insufficiency on LM. According to the reference values of the method, VD deficiency and/or insufficiency were defined as a serum 25(OH)D level of < 25 ng/ml.20 Regarding the protocol of the obstetric clinical follow-up of the Obstetrics and Gynecology Department of the same university, a weekly dose of 50,000 IU oral vitamin D3 had been given to all pregnant women with 25 (OH)D levels below 25 ng/ml for eight weeks at the time of first admission for gestational control (sixth to 10th weeks of gestation). All the patients receiving VD supplementation attended follow-up at the end of the eight week of treatment and at the third and sixth months after conception, and treated with the same regimen according to the re-evaluation of laboratory findings. All the patients with normal VD levels participating to the study protocol, attended also the routine follow-up schedule and had also been prescribed VD supplementation in OBGYN clinics while their level was determined below the normal range but the patients refused to take the medication due to their sociocultural or religious concerns or inadherence to the given replacement therapy.

All the volunteers were informed about the purpose of the study and signed a written informed consent form. Ethical approval for the study was obtained from the *Research* Ethics Committee of Medipol University (decision number: 10840098-772.02-6564/186).

Data Collection

Demographic data, including age, education level, smoking habits, and body mass index (BMI) at the first visit to the hospital from the sixth to 10th week of pregnancy (BMI-P) (, BMI at the time of presentation to the general surgery clinic during the lactation period (BMI-L) , gravida and parity of 132 patients were recorded. Other

birth- and breastfeeding-related data were lactation time, lactation frequency, preterm birth history, presence of nipple cracks, and a single or recurrent clinical and subclinical mastitis attacks. Laboratory parameters related to VD metabolism and treatment, including the VD level at the first visit to the hospital from the sixth to 10th week of pregnancy (VD-P), VD level at the time of presentation to the general surgery clinic during lactation (VD-L),calcium, phosphorus, alkaline phosphatase and vitamin B12 were also compared between the two groups. We reviewed the electronic medical charts of all patients and analyzed the demographic and laboratory data according to the treatment methodology and outcomes.

Statistical Analysis

The clinical data were compared between the groups. The data were analyzed using SPSS software, version 15.0 (SPSS Inc. Chicago, IL). The power analysis for the occurence of lactational mastitis in between the two groups was performed using G power 3.1.6 for Windows (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany). The minimum required size of the study population was calculated to be 125 subjects in for a large effect size with at the 95% confidence interval for $\alpha = 0.05$. The group sample sizes were determined pragmatically with all patients who met the criteria, agreeing to participate in the study over the four-month period.

The descriptive statistics were expressed as number and percentages for categorical variables, and mean, standard deviation, minimum and maximum values for numerical variables. Since the numerical variables met the normal distribution condition, the Mann-Whitney U test was conducted for the comparison of two independent groups. The percentages of the groups were compared using the chi-square analysis. The significant factors were further evaluated using the logistic regression analysis. The alpha statistical significance level was accepted as $p < 0.05$.

Results

When the results were examined, BMI-P and BMI-L of the patients who received VD replacement (Group 2) were statistically significantly higher than those that did not receive VD replacement (Group 1) ($p = 0.0037$ and $p = 0.004$, respectively). BMI-P and BMI-L were calculated as 24.09 ± 1.89/24.3-8.2 kg/m^2 and 24.80 ± 1.90/24.7-9.3, respectively for Group 1, and 30.06 ± 1.3/29.8-10.3 kg/m^2 and 31.29 ± 2.31/30.9-9.4, respectively for Group 2. No statistically significant difference was found in the remaining demographic characteristics (gender, education level, smoking habits, gravida, and parity) between the two groups (Table 1).

Table 2 shows the comparative birth- and breastfeeding-related characteristics of the two groups. The lactation time and frequency of the two groups were statistically similar [8.33 ± 1.81 (8-6) vs 8.43 ± 2.03 (8-6) and 7.45 ± 2.19 (8-9) vs 7.13 ± 1.79 (7-6)]. Although there was no statistically significant difference between the two groups in terms of the preterm birth rate; the rates of nipple crack, mastitis attacks, recurrent mastitis attacks, and abscess drainage were statistically significantly higher in Group 1 compared to Group 2 ($p = 0.021$, $p = 0.035$, $p = 0.016$, and $p = 0.043$, respectively) (Table 2).

Biochemical parameters related to the VD metabolism and treatment in the two groups are given in Table 3. When Groups 1 and 2 were compared, there was a statistically significant difference in terms of the VD-P and VD-L levels of the patients. Although VD-P was found to be significantly lower in Group 2, the VD-L level of this group was significantly higher after appropriate treatment. The remaining biochemical parameters related to the VD metabolism and treatment showed no significant difference between the groups (Table 3).

The paired test results of the VD-P and VD-L values are presented in Table 4. While the VD-L value was significantly decreased in Group 1, it was significantly increased in Group 2 ($p = 0.023$ and $p = 0.000$, respectively). No statistically significant difference was observed between the VD-P and VD-L levels of the patients who developed LM, whereas there was a considerable statistically significant difference between these levels among the patients who did not develop LM ($p = 0.675$ and $p = 0.000$, respectively) (Table 4).

According to the binary logistic regression analysis model constructed based on all parameters related to LM to identify factors that predicted the development of LM, the VD level model was statistically significant in determining patients with mastitis attacks ($p < 0.05$). When the odds ratio [Exp (B)] coefficients were examined, a higher BMI-L (> 25kg/m^2) increased the incidence of mastitis attacks by 1.5 times and nipple cracks by 1.2 times while an increased rate of VD use and a higher VD-L level (> 25 ng/ml) decreased the mastitis attack incidence by 1.2 and 1.9 times, respectively. The model established as a result of the logistic regression analysis correctly classified the patients without a mastitis attack at a rate of 91.3% and those with a mastitis attack at a rate of 72.5%. The overall success rate of the model was calculated as 85.6% (Table 5).

Discussion

Global health policies attempt to promote breastfeeding in a large part of the society, and thus play an active role in achieving innovative and continuous progress in maternal and infant health. They also maintain confidence in exclusive breastfeeding by eliminating factors that render this process difficult and troublesome [1, 2]. One of the most important factors that undermine efforts to improve breastfeeding rates and duration worldwide and contribute to early weaning from breastfeeding is LM, a state of painful, inflammatory condition expressing a systemic illness with high fever, aches and chills mimicking flu-like symptoms, and red, tender, hot, and swollen areas of the breast [8-10, 22]. Not surprisingly, especially women who experience severe or recurrent attacks of LM tend to cease breastfeeding earlier than their healthy counterparts [4, 5]. In light of this finding, many studies have been conducted to evaluating protective factors to prevent development of LM in breastfeeding women. Mother- and child-related factors, including nutritional deficiencies, suckling habits, nipple problems, and even a family history of LM have been separately analyzed by several studies to define both

Table 1. Sociodemographic data of the all the participants according to VD use

		VD use				
		Absent		Present		
		n = 49	37.1%	n = 83	62.9%	p
Age*, year		30.37 ± 6.34/29-24		30.31 ± 6.01/30-26		0.970
Education level	Illiterate	6	12.24	4	4.82	0.357
	Primary school	8	16.33	20	24.1	
	High school	22	44.9	35	42.17	
	University	13	26.53	24	28.92	
Smoking°	No	37	75.51	69	83.13	0.200
	Yes	12	24.49	14	16.87	
BMI-P*		24.09 ± 1.89 / 24.3-8.2		24.80 ± 1.90 / 24.7-9.3		0.037
BMI-L*		30.06 ± 1.93 / 29.8-10.3		31.29 ± 2.31 / 30.9-9.4		0.004
Gravida*		2.94 ± 1.49 / 3-6		2.40 ± 1.33 / 2-6		0.074
Parity*		2.04 ± 0.93 / 2-4		1.99 ± 0.97 / 2-4		0.677

VD: vitamin D, BMI-P: body mass index during pregnancy, BMI-L: body mass index during lactation, *Mean ± SD (median-range)-Mann-Whitney U test, °Pearson's chi-square test $p < 0.05$ considered statistically significant

Table 2. Birth- and breastfeeding-related characteristics of the patients according to VD use

	VD use				
	Absent		Present		
	Mean ± SD (min-max)		Mean ± SD (min-max)		p
Lactation time (month)	8.33 ± 1.81 (8-6)		8.43 ± 2.03 (8-6)		0.858
Lactation frequency (per day)	7.45 ± 2.19 (8-9)		7.13 ± 1.79 (7-6)		0.384
	n	%	n	%	p
Preterm birth < 37 w (%)					0.071
No	36	73.47	71	85.54	
Yes	13	26.53	12	14.46	
Nipple crack (%)					*0.021
No	26	53.06	60	72.29	
Yes	23	46.94	23	27.71	
Mastitis attack (%)					*0.035
No	29	59.18	63	75.9	
Yes	20	40.82	20	24.1	
Recurrent attacks (%)					*0.016
No	41	83.67	74	89.16	
	8			10.84	
YesAbscess drainage (%)NoYes	43	16.3387.7612.24	9794	95.18	*0.043
	6			4.82	

VD: vitamin D, SD: standard deviation. Mann-Whitney-U test, chi-square test. *$p < 0.05$ considered statistically significant

Table 3. Biochemical analyses of the patients according to VD use

	VD use		
	Absent	Present	
	Mean ± SD (median-range)	Mean ± SD (median-range)	p
VD-P	29.1 ± 9.45/21-41.4	22.73 ± 8.36/21.7-35.1	*0.033
VD-L°	24.38 ± 10.63/23.1-46.2	34.79 ± 10.85/33.5-50.6	* < 0.001
Calcium	8.98 ± 0.27/9.0-1.4	8.99 ± 0.27/9.0-1.4	0.837
Phosphor	3.69 ± 0.38/3.7-2.3	3.64 ± 0.38 / 3.6-2.3	0.438
ALP	80.2 ± 14.86/83-68	79.57 ± 16.09/83-68	0.914
Vit B12°	331.16 ± 172.33/316-741	334.43 ± 168.05/332-678	0.915

VD-P: Vitamin D during pregnancy, VD-L: Vitamin D during lactation, ALP: alkaline phosphatase, T-test, ° Mann-Whitney U test

Table 4. VD change analysis during pregnancy and lactation (Mean ± SD/median-range)

	VD-P	VD-L	p
Control	29.10 ± 9.45 / 21.00-41.4	24.38 ± 10.63 / 23.10-46.2	0.023*
VD use	22.73 ± 8.36 / 21.70-35.1	34.79 ± 10.85 / 33.50-50.6	0.000*
Mastitis (absent)	23.71 ± 9.57 / 22.05-41.9	35.12 ± 10.87 / 33.85-51.1	0.000*
Mastitis (present)	20.93 ± 6.14 / 20.25-26.4	21.29 ± 7.73 / 21.15-31.6	0.675
Total	22.87 ± 8.75 / 21.50-41.9	30.93 ± 11.86 / 29.50-62.3	0.000*

VD-P: vitamin D during pregnancy, VD-L: vitamin D during lactation. *p < 0.05 statistically significant. ** Paired t-test *** Paired Wilcoxon test

Table 5. Binary logistic regression analysis of the variables related to LM

	β coefficient	SE	Wald	df	p	Exp(B)
Higher BMI-L (> 25kg/m^2)	0.288	0.136	6.111	1	0.020*	1.475
Nipple crack	0.155	0.054	8.227	1	0.004*	1.168
Higher VD-L (> 25 ng/ml)	-0.276	0.056	23.971	1	0.001*	0.759
VD use	-1.634	0.973	45.643	1	0.001*	0.453
Constant	-5.277	3.599	2.149	1	0.143	0.005

SE: standard error, BMI-L: body mass index during lactation, VD-L: vitamin D during lactation

potential predisposing and protective factors to compose a risk assessment model for the prediction of women at higher risk of developing LM [4, 5, 9, 11, 23, 24].

Most studies conducted in the last two decades have demonstrated that protecting skin integrity by preventing the formation of nipple cracks and strengthening host immune response by immunomodulators, including probiotics, vitamins, and minerals have been found to be the most effective ways to prevent LM [9, 11, 23-26]. An optimal protective agent would possess both of these properties, helping to maintain skin integrity and effectively modulating the immune system to defend against potential pathogens targeting the human defense system. VD, having both features, is one step ahead of other immunomodulators in the human metabolism, and can be easily measured in body concentrations and supplemented in case of deficiency. VD strengthens the innate immune response by stimulating cell proliferation and differentiation. It has a well-defined anti-inflammatory effect on adaptive immunity mediated by human T cells. Furthermore, it has a highlighted, complex and dynamic role in enhancing the clearance mechanisms of pathogens of bacterial or viral origin, which threaten bodily functions.15 The protective effects of VD has been intensively studied in a wide variety of bacterial, viral and fungal infections, providing evidence supporting the idea that the prognosis of many infectious diseases can be positively reversed by the daily or weekly supplementation of VD [13, 15, 27-29]. Although an undeniable number of studies have investigated the role of VD as an immune-modulator agent in different infectious diseases, to the best of our knowledge, the current study is the first to analyze the effects of VD supplementation during pregnancy on the development of LM.

Multiple micronutrient deficiencies commonly co-exist in pregnant and lactating women, especially in developing countries. Food sources of VD are negligeable, and VD intake during pregnancy is not ordinarily recommended during routine obstetric follow-up.30 Not surprisingly, in the current study conducted in a university hospital, in which all pregnant women were examined for the VD level at their first visit to the obstetric clinic and received appropriate VD supplementation if needed, nearly 1/3 of the patients participating in the study (63%) were supplemented by VD during the early periods of pregnancy. According to our results, the patients treated with VD supplements due to VD deficiency had significantly higher BMI during both pregnancy and lactation, indicating that increased BMI is also associated with increased requirements of micronutrients, especially those acting to maintain optimal health through pleiotropic effects. Higher prevalence of VD deficiency and higher requirements for VD supplementation in obese population are well-documented in many previous studies31, 32, and the current study showed significant parallelism to this previously reported negative correlation . Higher BMI during pregnancy and lactation seems to be associated with decreased VD concentrations due volumetric dilution, and the need for VD supplementation is notably increased in this patient group [32].

This study also showed that although there was no difference in terms of lactation frequency and duration between the two groups, a statistically significant decrease was observed in the rates of nipple cracks, single or recurrent mastitis attacks, and abscess drainage in the patient group supplemented with VD. When all these findings were evaluated in light of the literature data, it can be suggested that VD may have been effective in reaching these results through many different pathways, including strengthening of the epithelial barrier function, preservation of skin barrier integrity ending up with less nipple crack occurence, modulation of a positively innate and adaptive immune system, and upregulation of anti-microbial peptides with bactericidal activity against S. aureus, the most commonly isolated microorganism in LM [13, 15, 20, 33, 34]. Another important finding of the study was the powerful relationship between VD supplementation and VD-L demonstrated by a significant increase in the VD-L levels compared to the VD-P levels in the supplemented group. Unfortunately, a similar increase was not detected in the control group, although most women paid attention to receiving sufficient through their diet and sunlight exposure

during pregnancy and lactation. The remaining biochemical parameters involved in the VD metabolism were not found to be affected by VD supplementation since they did not significantly differ between the two groups. This suggests that during pregnancy when the bodily needs inadvertently increase to support fetal growth, changes in the VD level should be monitored and an optimal VD level should be maintained through well-organized supplementation programs.

The data analysis of the current study revealed that a significant increase in the VD levels from pregnancy to lactation was clearly associated with a lower incidence of mastitis attacks. As mentioned previously, LM is characterized by an inflammatory state primarily involving the breast but it also acts like a systemic infection invading all body compartments, mimicking a mild form of sepsis [4, 5, 10]. VD has great potential to designate the bodily response against pathogenic microorganisms targeting the defense system, with its deficiency contributing to the pathophysiology of both inflammatory skin disorders and several systemic infectious diseases [15, 20, 27-29, 35]. Studies addressing the association between the VD level and occurrence of local and systemic infections have revealed that not only geographic, seasonal and diet-integrated VD variations but also routine VD follow-up and supplementation in the presence of deficiency can positively alter host response against infections. In addition, it has been reported that even in a population determined to have borderline VD levels, VD supplementation is protective against systemic infectious and inflammatory conditions [18, 29].

The starting point of this study was to analyze the possible preventive effects of VD supplementation during pregnancy and the effects of increased VD levels on the development of LM. In addition, this study evaluated the most commonly identified variables that were considered to be associated with LM development and their relationship with VD use and the VD-L level. In this context, the regression analysis undertaken to create a risk map revealed that VD supplementation during pregnancy and a higher VD-L level had a clear protective effect against LM. It should also be noted that the protective effect of VD supplementation itself seems to be higher compared to VD-L, which can be considered to provide significant evidence of routine clinical requirement of VD supplementation during these periods. Another important result of this study is that VD-P did not have any effect on the development of mastitis attacks, which indicates the need for VD supplementation in all pregnant women to ensure their own health and indirectly contribute to the health of their future children. Our data analyses also revealed, consistently with the literature, that increased BMI-L and the presence of nipple cracks were associated with an increased risk of LM at the ratios of 1.3 and 1.2 times, respectively. Considering these findings, VD supplementation and the resulting higher VD-L level can provide dual protection against LM through both immune system pathways and its effects on obesity and skin integrity [13, 15, 31, 32].

The strengths of this study are that it was the first to analyze the effect of the VD level and VD replacement on LM conducted in a baby-friendly university hospital where pregnancy follow-ups are strict and cover a wide range of examinations and replacement treatments according to laboratory measures until the end of the sixth month of lactation, including maternal vitamin levels. However, this study also has certain limitations. First, all the patients received the same VD replacement treatment, but different types of VD replacement models may act differently. On the other hand, although the literature contains several studies conducted to predict the amount of VD required to normalize the maternal and infantile VD status, the medical community has unexceptionally accepted that there is no 'one and only' ideal supplementation to achieve robust VD sufficiency that would allow sufficient VD content through human breast milk in lactating women.36, 37 Secondly, since the study design was retrospective and conducted with participants in lactation period attending to general surgery clinic with various complaints, grouping may create a bias over the results about the effect of VD levels and efficacy of VD replacement on LM. Since it is ethically impossible to conduct a prospective study in VD deficient patients in gestational period, grouping as replacement and non-replacement parties, further prospective randomized studies with healthy participants with normal VD levels at the early gestational period, divided into groups as those who would use VD supplementation and those who would not receive this treatment would reinforce the results of our study. Finally, the study period may have had an effect on the VD values of the patients, since some diseases have been previously associated with seasonal variations in VD.

In conclusion, pregnant and lactating women, especially the latter, are more sensitive to the effects of VD deficiency than the general population. In this study, overlooked or untreated VD deficiency was found to be a possible risk factor for the development of LM, a condition specific to the lactation period. Although VD deficiency is much more commonly seen among breastfeeding women compared to non-breastfeeding counterparts and even this situation alone makes VD replacement mandatory, including normal healthy lactating individuals with sufficient VD levels may benefit from the positive effects of replacement therapy. We consider that concerted efforts are necessary to reduce this manageable risk factor, especially by promoting a well-designed and schematized replacement treatment based on VD levels started from the early pregnancy period without considering the initial VD levels of the individual. Future studies with a prospective design should investigate whether routine VD replacement applied from the early gestational period to the end of exclusive breastfeeding can decrease the likelihood of possible occurrence of nipple disorders and LM. This presents a tremendous opportunity for early interventions to prevent LM and improve the quality of life of lactating women during the most sensitive period of their lives.

Ethics approval

Ethics committee approval was received for this study from the *Research* Ethics Committee of Medipol University (decision number: 10840098-772.02-6564/186)

Availability of data and material

Data supporting the findings of this study are available from the corresponding author [P. Basim] on request.

Authors' contributions

Concept – P.B., S.B.; Design – P.B., D.A.; Supervision – P.B., D.A; Resources – P.B.; Data Collection and/or Processing –P.B., D.A.; Analysis and/ or Interpretation – P.B, D.A..; Literature Search – P.B., S.B; Writing Manuscript – P.B., S.B.; Critical Review – P.B.

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