



# Association between Maternal and Infant Serum Vitamin D and Food Sensitization

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## ABSTRACT

This study aimed to determine the association between maternal and infant serum vitamin D levels. The association between serum vitamin D level and sensitization to food allergens in infants at the age of 4 months was investigated. Mother-child pairs were recruited at the delivery room of Thammasat University Hospital. Blood samples for 25-hydroxy vitamin D levels were obtained from mothers at delivery. The infants were scheduled to visit at the age of 4 months. Blood samples were taken from the infants for measuring serum 25-hydroxy vitamin D level and specific IgE to food allergens including cow's milk protein, egg white, and soy protein. There were 60 mother-child pairs in the study. The prevalence of maternal vitamin D deficiency at delivery was 53.3 percent (95% confidence interval: 40.0%-66.3%). For infants at 4 months, the prevalence of vitamin D deficiency was 18.8 percent (95% confidence interval: 8.9%-32.6%). Infants born from mothers who had vitamin D deficiency at delivery themselves had a higher prevalence of vitamin D deficiency ( $p=0.012$ ) than those from mothers without vitamin D deficiency. They were more likely to have sensitization to cow's milk protein at the age of 4 months. In conclusion, the impact of vitamin D deficiency in pregnant mothers was documented. There was a positive association between maternal and infant serum 25-hydroxy vitamin D concentrations. Pregnant mothers with vitamin D deficiency were associated with vitamin D deficiency in their infants at the age of 4 months.

**Keywords:** Cow's milk protein; Infants; pregnancy; Sensitization; Vitamin D deficiency; White egg protein

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## 1. Introduction

There has been growing interest in the influence of maternal vitamin D intake during pregnancy on the development of allergic diseases in children [1]. During pregnancy, the fetus is exposed to vitamin D through cord blood supply and the placenta [2]. Vitamin D has immunomodulatory effects on allergen-induced inflammatory pathways via a vitamin D receptor expressed on a variety of immune cells including B cells, T cells, dendritic cells and macrophages [3]. An inverse association between maternal vitamin D intake during pregnancy and risk of the development of atopic diseases in offspring has been reported [4-5]. Maternal diet during pregnancy has been associated with early IgE sensitization and subsequent development of allergic diseases in children [6-7].

Based on epidemiological data, the increase in food allergen sensitization parallels the increase of vitamin D deficiency [8]. Vitamin D deficiency may increase susceptibility to infections and alter intestinal microbial ecology, contributing to abnormal intestinal barrier permeability. These factors might promote maladaptive allergic responses to food antigens and result in food allergy in genetically susceptible subjects.

Vitamin D deficiency, defined as a serum 25-hydroxy vitamin D level of less than 20 ng/mL, has been a public health problem globally [9]. Both children and pregnant women are at risk of vitamin D deficiency [10]. However, the association of maternal vitamin D status with allergen sensitization and atopic disease development remains uncertain [11]. It has been reported that vitamin D is able to both enhance and inhibit the differentiation of plasma cells and the production of IgE [12-13]. This study aimed to determine association between maternal and infant serum vitamin D levels.

The association between serum vitamin D level and sensitization to food allergens in infants at the age of 4 months was investigated.

## 2. Materials and Methods

Mother-child pairs were recruited at the delivery room of Thammasat University Hospital between August 2018 and November 2018. Inclusion criteria included maternal age more than 18 years, no pregnancy complications, and singleton delivery of term infants with a birth weight of more than 2,500 grams. Mothers with underlying diseases including chronic liver disease, chronic renal diseases, nephrotic syndrome, vitamin D mal-absorption, diabetes mellitus and malignancy, or were on anti-epileptic drugs or systematic steroids were excluded from the study. Neonates with congenital malformations and those who were admitted to high-risk rooms or neonatal intensive care units were also excluded from the study. Blood samples for 25-hydroxy vitamin D levels by enzyme-linked immunosorbent assay (ELISA) were obtained from mothers at delivery. Demographic and parental history of allergic disease data were collected by parental-administered questionnaire. The infants were scheduled to visit at the age of 4 months. Then, blood samples were taken from the infants for serum 25-hydroxy vitamin D level ELISA measurement and specific IgE to food allergens including cow's milk protein, egg white, and soy protein by ImmunoCAP (Phadia, Uppsala, Sweden). The threshold for a reaction to be considered sensitization to a specific allergen was set at 0.35 kUA/L. Vitamin D deficiency was defined as having a serum 25-hydroxy vitamin D level of less than 20 ng/ml. This study was approved by the ethics committee of Thammasat University No1.

### 3. Statistical Analysis

Quantitative data are presented as mean and standard deviation. Qualitative data are presented as numbers of subjects and percentages. Prevalence of vitamin D deficiency and sensitization to food allergens were calculated and are presented with the 95% confidence intervals. Correlation between maternal and infant serum 25-hydroxy vitamin D levels are presented as scatter plots, with correlation coefficients calculated accordingly. Fisher's exact test was used to test the association between categorical variables, with a significance level of 0.05. Odds ratio was used to assess the association between sensitization to cow's milk and egg white proteins in infants at 4 months.

### 4. Results and Discussion

There were 60 mother-child pairs in the study; of these, 48 infants were available at the 4-month follow-up date, for measuring serum IgE to food allergens and serum 25-hydroxy vitamin D level. Maternal, family and infant characteristics are presented in Table 1. All infants in the study were term, with a mean birth weight of 3,214±304 grams. The prevalence of maternal vitamin D deficiency at delivery was 53.3 percent (95% confidence interval: 40.0%-66.3%). Regarding infants at 4 months, the prevalence of vitamin D deficiency was 18.8 percent (95% confidence interval: 8.9%-32.6%). The prevalence of cow's milk protein and egg white protein sensitizations by serum specific IgE assays were 22.9 percent (95% confidence interval: 12.0%-

37.3%) and 10.4 percent (95% confidence interval: 3.5%-22.7%), respectively. All had soy-specific IgE serum levels < 0.35kUA/L.

Data for the relationship between infant serum 25-hydroxy vitamin D concentrations at 4 months and maternal serum 25-hydroxy vitamin D concentrations are presented as a scatter plot (figure 1), having a correlation coefficient of 0.435. At the age of 4 months, infants of mothers who had vitamin D deficiency at delivery had a higher prevalence of vitamin D deficiency (10%) than those without vitamin D deficiency (25%) with  $p = 0.012$  as detailed in Table 2.

For infants with vitamin D deficiency at the age of 4 months, there was no statistically significant impact on sensitization to cow's milk protein (odds ratio = 1.9) or egg white protein (odds ratio = 3.4) (Table 3).

Maternal vitamin D deficiency (<20 ng/ml) is rather common, as evidenced by the 53.3 percent prevalence seen in this study. This finding is consistent with the high prevalence reported globally: 21.2% in the UK, 44.6% in Belgium, and 83.6% in China [14-16]. A strong correlation between the serum 25-hydroxy vitamin D level of pregnant mothers and their newborns has been reported [17]. The 25-hydroxy vitamin D has the ability to cross the placenta and expose the fetus to vitamin D during pregnancy [18]. Since many pregnant mothers worldwide were shown to have deficient vitamin D status, this consequence may result in deficient vitamin D levels in their newborns [10].

**Table 1.** Maternal, family and infant characteristics.

Characteristics	N	%
<b>Maternal and family (N=60)</b>		
Highest education among parents		
Primary school	7	11.7
Secondary school	32	53.3
Bachelor's degree or higher	21	35.0
Paternal allergy	20	33.3
Maternal allergy	18	30.0
Smoking during pregnancy	1	1.7
Passive smoking at home	29	48.3
Maternal age in years	26.2±3.8	
Maternal vitamin D deficiency	32	53.3
Serum 25-hydroxy D level in ng/ml	21.7±8.7	
Gestational age in weeks	38.2±1.9	
<b>Infant characteristics at birth (N=60)</b>		
Birth weight in grams	3214±304	
Boys	28	46.7
The first child	31	51.7
<b>Infant characteristics at 4 months (N=56)</b>		
Exclusive breast feeding	22	39.3
History of eczema	12	21.5
Vitamin D deficiency (N=48)	9	18.8
Serum 25-hydroxy vitamin D level in ng/ml	27.2±7.0	
<b>Allergen sensitization* (N=48)</b>		
cow's milk protein	11	22.9
egg white protein	5	10.4
soy protein	0	0

Note: \*Serum specific IgE level &gt; 0.35 kUA/L

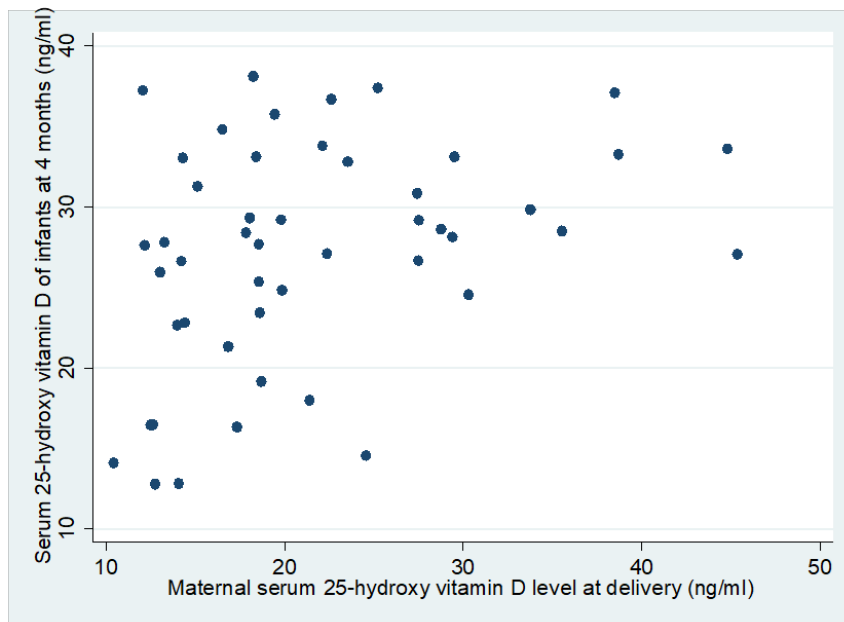
**Table 2.** Association of vitamin D deficiency between mothers at delivery and infants at 4 months (N=48 pairs).

Vitamin D status of infants at 4 months	Vitamin D status of mothers at delivery		P-value
	No deficiency	Deficiency	
No deficiency (n=39)	18 (90.0%)	21 (75%)	0.012
Deficiency (n=9)	2 (10.0%)	7 (25.0%)	
Total	20 (100%)	28 (100%)	

**Table 3.** Association between vitamin D deficiency in infants at 4 months and sensitization to cow's milk and egg white protein in infants at 4 months.

Vitamin D status	Sensitization *	No Sensitization*	Odds ratio (95% confidence interval)	P- value
To cow' milk protein				
No deficiency (n=39)	8 (20.5%)	31 (79.5%)	1.9 (0.4-9.8)	0.414
Deficiency (n=9)	3 (33.3%)	6 (66.7%)	-	
To egg white protein				
No deficiency (n=39)	3 (7.7%)	36 (92.3%)	3.4 (0.2-35.1)	0.198
Deficiency (n=9)	2 (22.2%)	7 (77.8%)	-	

Note: \*Specific IgE level by the cutoff value of 0.35 kUA/L.



**Fig. 1.** Scatter plots between serum 25-hydroxy vitamin D level of infants at 4 months and maternal serum 25-hydroxy vitamin D levels at delivery (Correlation coefficient = 0.435).

This study found an association between maternal and infant 25-hydroxy vitamin D levels ( $r=0.435$ ,  $p<0.001$ ), which is consistent with the findings from a study in Greece ( $r=0.626$ ,  $p<0.001$ ) [19]. Children born to mothers with vitamin D deficiency appeared to have persistent and significantly lower serum vitamin D levels, compared to those with sufficient vitamin D levels [20–21]. In this study, maternal vitamin D deficiency and infant vitamin D deficiency seemed to be associated with a higher prevalence of food sensitization at the age of 4 months. Vitamin D deficiency might contribute to early-life sensitization by further compromising the maturation of the infant immune system [20]. However, no consistent data have addressed the relationship between maternal vitamin D levels and allergen sensitization in infants. Some authors have reported that maternal vitamin D levels were inversely associated with sensitization to food allergens [20–22]. On the other hand, a higher risk for food sensitization in infants was seen in mothers with high vitamin D levels during pregnancy [17]. One study even showed that low

vitamin D levels ( $<20$  ng/ml) and high vitamin D levels ( $>40$  ng/ml) at birth were associated with total serum IgE concentrations and aeroallergen sensitization in early childhood [23]. Vitamin D deficiency might impair epithelial barrier integrity. This leads to increased and inappropriate mucosal exposure to food antigens and also a pro-sensitization immune imbalance that compromises immunological tolerance [24].

The strength of this study comes from its longitudinal design, allowing temporality in mother-child pair measurements of serum vitamin D levels and specific IgE levels. Limitations of this study include the relatively small sample size of only 48 mother-child pairs available for analysis, with limited power to detect a statistically significant association for sub-analyses. This study did not assess clinical outcomes. The follow-up period of 4 months may not have been long enough to detect allergic diseases throughout the childhood period. Future studies of vitamin D supplementation in mothers during pregnancy may be beneficial

to establish the role of vitamin D in the development of atopic diseases in children.

## 5. Conclusion

These results address the impact of vitamin D deficiency in pregnant mothers. A positive association between maternal and infant serum 25-hydroxy vitamin D levels was documented. Deficient vitamin D status in pregnant mothers may result in deficient vitamin D status in newborns and subsequent sensitization to food allergies at the age of 4 months.

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