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Maternal factors associated with neonatal vitamin D deficiency

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Abstract

Background: An adequate maternal vitamin D (vitD) intake is rarely achieved in actual practice. The aim of this study was to assess maternal factors associated with neonatal vitD deficiency.

Methods: This is a single-institution prospective case-control study. Consecutive single-birth neonates admitted between September 2014 and February 2015 were prospectively enrolled. Serum 25-hydroxyvitamin D (25(OH) D) concentrations were measured by spectrometry. The associations between neonatal vitD deficiency (defined as 25(OH)D <15 ng/mL) and several maternal characteristics, including body mass index (BMI) at delivery, education, health insurance status, birth season, sun exposure time, egg consumption, and vitD supplementation during pregnancy, were examined using multivariable logistic regression and their respective odds ratios (ORs) reported.

Results: A total of 125 mother-infant dyads were enrolled, with a gestational age of 36.8 ± 2.7 weeks. Fifty-six percent (70/125) of the neonates had vitD deficiency. Maternal factors that were significantly associated with vitD deficiency included winter birth, insufficient sun exposure time, high maternal BMI at delivery, insufficient egg consumption, insufficient vitD supplementation during pregnancy, and disadvantaged health insurance. Disadvantaged insurance status and insufficient vitD supplementation during pregnancy were the two most influential factors of neonatal vitD deficiency, with an OR of 7.5 (95% confidence interval [CI], 2.0–37.6) and 7.0 (95% CI, 2.7–20.7), respectively.

Conclusions: Neonatal vitD deficiency is very rampant. An individualized vitD supplementation strategy may be developed by taking into consideration pregnant women's socioeconomic status and lifestyles.

Keywords: associated factors; infant; neonate; pregnant woman; vitamin D deficiency.

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Introduction

Vitamin D (vitD) plays important pleiotropic roles, especially in calcium metabolism and bone health. Recent publications have also revealed its utility in maintaining physiological functions and general health. Strictly speaking, vitD is not a "real" vitamin but a preprohormone primarily made from the skin under ultraviolet B (UVB) radiation with a wavelength ranging between 280 and 320 nm [1]. In inland areas, the natural diet typically does not provide physiologically sufficient vitD.

An adequate maternal vitD intake is rarely achieved in actual practice. Although the recommended dose of vitD supplementation during pregnancy is somewhat uniform, the actual dose taken is variable among pregnant women for a variety of reasons. An optimal amount of vitD intake should meet the demand of both the mother and the fetus, but uncertainty exists mainly on how much vitD a pregnant woman generally obtains from dietary intake and from sunshine exposure and whether vitD supplementation should be an individualized practice. Several previous studies have examined the associated factors of neonatal vitD level. However, some of the results were conflicting.

Therefore, the present study sought to examine maternal factors associated with neonatal vitD deficiency in our institution. Several clinically modifiable factors of the mother were investigated for the purpose of clinical meaningfulness.

Materials and methods

The study was approved by the Institutional Review Board of Peking Union Medical College Hospital (PUMCH), Beijing, China (Protocol Identification: ZS-842).

Setting, eligibility, and subject enrollment

PUMCH is a tertiary general hospital with a level IIIB neonatal intensive care unit (NICU). It is a perinatal referral center offering maternal and neonatal care for patients from Beijing.

The inclusion criterion was singleton infants of all gestational ages admitted to our newborn intensive care unit from September 2014 to February 2015 and their mothers. Beijing is located on latitude N39°.

Exclusion criteria included pregnant women with chronic diarrhea, liver diseases, kidney diseases, parathyroid diseases, other calcium-modifying conditions, and concurrent corticosteroid treatment and neonates with chromosomal anomaly, internal organ anomalies, or congenital metabolic diseases.

After delivery, an interviewer-administered questionnaire was used to collect maternal information, including education, prenatal vitD intake, duration of sun exposure per day, and prenatal number of eggs consumed per week. Medical records were reviewed to ascertain maternal age, prepregnant and prenatal history, length of gestation, prenatal weight and height, and health insurance status. Venous blood samples of neonates were obtained within 48 h of birth.

Definitions of the studied clinical factors

The level of serum 25-hydroxyvitamin D (25(OH)D) was measured by isotope dilution ultra-performance liquid chromatography tandem mass spectrometry, which is currently the gold standard for measuring serum 25(OH)D level [2]. VitD deficiency was defined as <15 ng/mL. In the present study, the vitD level was binarily defined as with vitD deficiency versus without (≥15 ng/mL).

Maternal age was binarily categorized as younger than versus older than or equal to 35 years (Table 1). Similarly, prenatal vitD intake, duration of sun exposure per day, and prenatal number of eggs consumed per week were binarily defined as sufficient versus insufficient, using 600 IU per day, 40 min per day, and 7 eggs per week, respectively, as the cutoffs. Maternal educational level was defined as college and above versus high school/professional school and below. Maternal body mass index (BMI) was defined as high (BMI at delivery >27) versus low. Birth season was defined as autumn (from September to November) versus winter (from December to February).

In the study population, health insurance plans included three types dependent upon the degree of government financial support and the geographic region of the individual (urban vs. rural). They were, in the order of increasing patient co-payment, (1) government

Table 1: Maternal characteristics by neonatal vitD level in the 125 mother-infant pairs.

	VitD deficiency (n=70)		Without vitD deficiency (n=55)		χ^2	p-Value
	n	%	n	%		
Age, years						
<35	52	74.3	33	60	2.89	0.09
≥35	18	25.7	22	40		
Maternal BMI						
>27	31	44.3	39	70.9	8.86	0.003[a]
≤27	39	55.7	16	29.1		
Education						
College and greater	50	72.9	50	90.9	7.31	0.007[a]
Less than college	20	27.1	5	9.1		
Health insurance						
Advantaged plan	49	70	51	92.7	9.94	0.002[a]
Disadvantaged plan	21	30	4	7.3		
Season of birth						
Winter	54	77.1	33	60	4.28	0.04[a]
Autumn	16	22.9	22	40		
VitD supplementation						
Insufficient	47	67.1	20	36.4	11.73	<0.001[a]
Sufficient	23	32.9	35	63.6		
Sun exposure time						
Insufficient	63	90	38	69.1	8.68	0.03[a]
Sufficient	7	10	17	30.9		
Egg consumption						
Insufficient	27	38.6	10	18.2	6.14	0.01[a]
Sufficient	43	61.4	45	81.8		

[a]Statistically significant.

employee insurance scheme (GIS), which covers employees of the government and other public institutions such as schools and hospitals [3]; (2) urban employee basic medical insurance (UEBMI), a plan for general urban public and private sector employees [4]; and (3) new rural cooperative medical scheme (NCMS), which is specifically for peasants living in rural areas.

The insurance status in the present study was operationally defined as two categories as follows: (a) advantaged insurance status, which means having a GIS or UEBMI, or (b) disadvantaged insurance status, which includes having an NCMS or being uninsured.

Examining the association between vitD deficiency and clinical factors

The association between vitD deficiency and clinical factors was examined in two steps. First, bivariate inferential analysis was performed to compare each clinical factor between the two categories of vitD level (with vitD deficiency vs. without). Then, the clinical factors significantly associated with vitD deficiency, as identified in the first step, were selected for a multivariable logistic regression, demonstrating each factor's association with vitD deficiency after simultaneously adjusting for the other factors.

Statistical analysis

Descriptive statistics were reported as mean or median, dependent on whether the data are normally distributed. Paired-sample t-test and chi-square test were used to compare continuous and categorical data, respectively. Odds ratio (OR) was used as the output measure of the multivariable logistic regression to evaluate the strength of association between the clinical factors and vitD deficiency. R version 3.4.3 software (R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis and visualization. The α-value was set at 0.05.

Results

A total of 132 mother-infant pairs were enrolled. Of this cohort, two missed the blood test and another five did not complete the questionnaire, leaving 125 mother-infant pairs available for analysis.

The newborns in the 125 mother-infant pairs had a mean birth weight of 2697 ± 713 g (range, 775–4800 g) and a mean gestational age of 36.8 ± 2.7 weeks (range, 26–41.3). The average neonatal serum vitD level was 14.4 ± 6.7 ng/mL. VitD deficiency was noted in 56.0% (70/125) of the neonates.

In univariable analysis, seven maternal factors including health insurance, BMI, education, season of delivery, vitD supplementation, sun exposure time, and the amount of egg consumption were found to be significantly associated with the development of neonatal vitD deficiency, while maternal age was not (Table 1).

Table 2: Associations between neonatal vitD deficiency and maternal characteristics, shown by multivariable logistic regression[a], in the 125 mother-infant pairs.

	Adjusted odds ratio (OR)	95% CI	p-Value
Sun exposure time (insufficient)	6.8	2.0–26.8	0.003
Season of birth (winter)	2.9	1.0–8.9	0.057
Egg consumption (insufficient)	3.0	1.1–8.7	0.036
VitD supplementation (insufficient)	7.0	2.7–20.7	<0.001
Maternal BMI (high)	2.9	1.2–7.6	0.025
Insurance status (disadvantaged)	7.5	2.0–37.6	0.006

[a]Education as an input variable was removed from multivariable logistic regression through the "backward selection" process, as it was not significantly associated with vitD deficiency in the multivariable setting.

In multivariable logistic regression involving these seven variables, all factors except education were found to be independently significantly associated with neonatal vitD deficiency (Table 2, Figure 1). For maternal health insurance status, for example, the odds of neonatal vitD deficiency was increased 7.5-fold in families with disadvantaged insurance (95% confidence interval [CI], 2.0–37.6) compared with families with advantaged insurance status.

Discussion

More than half of the cohort of infants delivered in PUMCH between September 2015 and February 2016 were vitD deficient (56%). Neonatal vitD deficiency is associated with short duration of sun exposure, winter birth, insufficient egg consumption, high maternal BMI, insufficient vitD supplementation, and disadvantaged insurance status.

From our results, longer time of sun exposure during pregnancy was a major protective factor against neonatal vitD deficiency. This is in keeping with the results of previous observational studies. Most vitD biogenesis comes from the synthesis process, whereby 7-dehydrocholesterol is converted by the sun's UVB into vitamin D_3 in the skin [1]. In agreement with other reports, vitD deficiency was correlated with low sun exposure [5, 6]. Hypovitaminosis D is more likely to take place during winter months because of the ineffectiveness of the winter sun to facilitate vitD synthesis [7]. Similar patterns were reported in studies from other countries [8–12]. In winter, sunlight travels longer through the atmosphere where the UVB is absorbed to a greater degree. Moreover, because the average temperature in Beijing during winter months (December, January, and February) is typically below 0 °C [13], people usually

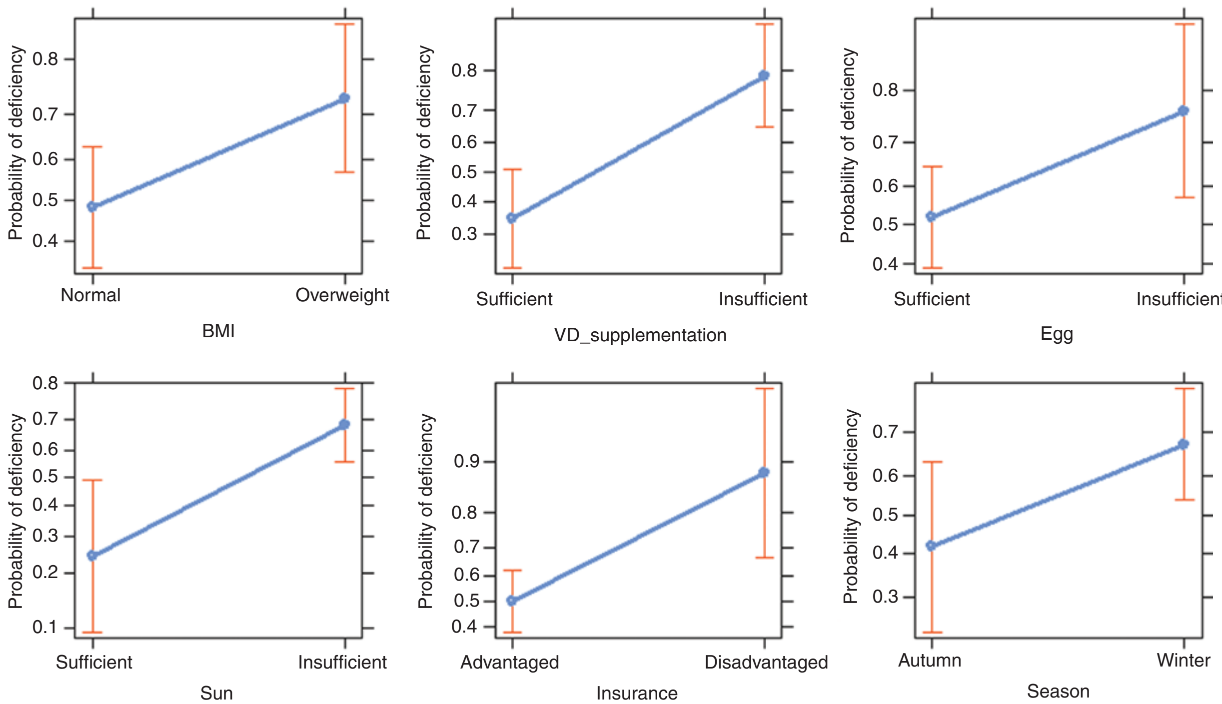

Figure 1: The relationship between maternal factors and neonatal vitD deficiency.
Each plot demonstrates a significant association, as identified using the multivariable logistic regression, between a clinical factor and vitD deficiency. A blue point indicates the predicted probability of having vitD deficiency given the neonate's status on a specific clinical factor, and the red bar crossing the blue point indicates the 95% CI of that probability. In the plot of "insurance" (the middle plot in the lower row), for example, the predicted probability of having vitD deficiency in the neonates without maternal insurance is greater than 85%, while in those with insurance, it is about 50%, which is a disparity of an odds ratio of 7.5. BMI, body mass index; VD supplementation, average dose of vitD supplement intake per day; egg, average weekly egg consumption; sun, average time of sun exposure per day; insurance, maternal health insurance status; season, season of birth.

dress much thicker and expose significantly less skin in winter than in other seasons. This can also lead to a significant birth season disparity in the infants' vitD level between autumn and winter.

Previous studies have demonstrated that vitD nutritional status can be improved by food fortification [14]. However, few commercial vitD-fortified foods are available in China, and residents of the inland areas of China seldom consume oily fish from the deep sea, which is naturally rich in vitD [15]. As an alternative, pregnant women in China typically eat eggs, Shiitake mushrooms, animal liver, and meat, which contain vitD but are more affordable and accessible, on a regular basis. Of these, eggs (the yolk part of each contains an average of 20 IU of vitD [16]) are relatively easy to record and were therefore used as an indicator of dietary source of vitD. Ganmaa et al. found that the 25(OH) D level was not associated with dietary factors in reproductive-age Mongolian women. However, the underlying reason may be that there is little access to vitD-rich foods in Mongolia, an inland country [17].

Our study showed that insufficient maternal vitD supplementation was associated with neonatal vitD deficiency. This result is in keeping with those of previous studies showing a correlation between the vitD level of infants and maternal vitD intake [6, 18]. Specifically, a study found that maternal vitD supplementation less than 600 IU/day could lead to neonatal vitD deficiency (serum vitD levels in cord blood <10 ng/mL) or insufficiency (10–20 ng/mL) [12]. The reason for the suboptimal supplemental vitD intake at the maternal end, however, remains unclear. It could be due to poor patient compliance or a lack of awareness at the physician end, both of which are not rare [8, 18–20]. In our study, for example, vitD supplementation in more than half of the mothers did not meet Chinese national recommendation of ≥600 IU/day, and among these women, 37% had never been prescribed vitD supplements and the others (63%) were noncompliant with the prescription. From our experience, it is somewhat concerning that many of those with poor compliance believe that vitD supplementation can simply be realized by sun exposure alone. In fact, most pregnant women can barely get enough vitD from sunlight for a variety of reasons including limited outdoor time, use of sun protection products, and air pollution in urban areas

[21]. When adequate sun exposure cannot be ensured, many physicians suggest that both children and adults need an average of 800–1000 IU of vitD supplementation per day [16]. Even in sunny Mediterranean areas, vitD supplementation was routinely recommended during pregnancy because of the local high prevalence of maternal and neonatal hypovitaminosis D [22–24].

From our results, high maternal BMI at delivery was associated with neonatal vitD deficiency. A previous study has shown that neonatal vitD deficiency was associated with high prepregnancy BMI in winter [5]. In the Odense Child Cohort (latitude 55.4°), neonatal vitD deficiency was associated with high maternal BMI at delivery [12]. The reason may be that as vitD is fat soluble, the more adipose tissue one has, the less the amount of circulating vitD [1]. Also, obesity may decrease the bioavailability of vitD [25].

This study is the first to examine the association between neonatal vitD level and maternal health insurance status. Our results showed that the newborns of mothers without any coverage or with NCMS (indicative of rural residents) were more likely to have vitD deficiency. It is thoroughly important to note that vitD supplements are generally not covered by health insurance in China. Therefore, this observed association cannot be merely attributed to affordability reasons. From our experience, these disadvantaged insurance plans, to some extent, reflect the underlying disadvantaged socioeconomic status of the patients – low income, poor health literacy, and limited access to healthcare information – that has been found to be related to both low vitD levels and poor adherence to vitD supplementation recommendations [22, 26].

In this study, maternal age was not associated with neonatal vitD deficiency and neither was maternal education level in the multivariable analysis. In a prior analysis, we also found that gestational age was not associated with neonatal vitD deficiency (data not shown). These findings are in keeping with previous studies, which have reported conflicting results regarding gestational age [18, 27, 28] and maternal education [11, 14] as potential risk factors of neonatal vitD deficiency.

Our motivation in this study was to identify several associated factors of neonatal vitD deficiency that are more modifiable than season and that are readily accessible in average clinical settings to provide a context for future studies aiming to develop individualized vitD supplementation regimens in pregnancy. The response to vitD supplementation is highly heterogeneous among individuals [29], even with daily doses as high as 600 IU, which may not be universally adequate for all pregnant women. The Endocrine Practice Guidelines Committee, for example, recommends that the daily intake of vitD for pregnant women between 19 and 50 years of age should be 1500–2000 IU [30]. From our results, an individualized vitD supplementation strategy may be developed by taking into consideration pregnant women's socioeconomic status and lifestyles.

The limitations of this study include the small sample size, single-institution setting, and potential recall bias due to the retrospective design of study questionnaires. Also, infants born in spring and summer as well as their mothers were not included, and this significantly limited the generalization of study results among the four seasons. Maternal BMI was recorded only at delivery, and data before pregnancy were lacking. Further studies with a larger sample size may be able to assess additional factors associated with neonatal vitD deficiency, such as multiparity. Also, the associated factors of patient compliance remain unknown and warrant further investigation.

In conclusion, vitD deficiency is prevalent in neonates born between September and February at PUMCH, Beijing, and is associated with a variety of maternal factors. On the basis of these results, our department partners with the Department of Obstetrics to provide health education pamphlets for pregnant women at the outpatient clinic to raise awareness on the necessity of early vitD level screening and supplementation starting in the first trimester of pregnancy. At the same time, our physicians are advised to pay attention to the risk factors identified in this study during patient counseling and work with public health professionals or social workers to address any relevant disparity if feasible.

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