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Effects of maternal commercial supplementation on 25-hydroxyvitamin D levels in newborns: a retrospective cohort study in a single center, Saitama, Japan, 2022–2023

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Abstract. Vitamin D (VD) insufficiency in pregnant women is a serious health problem worldwide. To prevent VD insufficiency during pregnancy, several guidelines recommend 600 IU/day VD for all pregnant women. In Japan, no national guidelines for preventing VD insufficiency have been implemented, and no study has evaluated adequate VD intake in pregnant women; however, the number of pregnant women taking commercial dietary supplements containing VD has increased in recent years. This study aimed to examine the effects of maternal commercial supplementation of VD on 25-hydroxyvitamin D (25(OH)D) levels in newborns. We retrospectively analyzed the serum 25(OH)D levels in 279 four-days-old newborns born at the Saitama City Hospital from 2022 to 2023. Newborns were classified into a supplement group (mothers who took VD-containing commercial supplements regularly throughout pregnancy; n = 103) and a non-supplement group (mothers who did not take any supplements during pregnancy; n = 176). The study findings revealed that serum 25(OH)D levels in newborns in the supplement group were higher than those in the non-supplement group (median [interquartile range]: supplement group 17.2 [14.6, 22.9] *vs.* non-supplement group 14.3 [11.6, 16.7], $p < 0.001$). In the supplement group, approximately 70% of newborns still showed VD insufficiency. Although the maternal use of VD-containing commercial supplements during pregnancy increased the serum 25(OH)D levels in newborns at four days of age, additional measures, such as VD supplementation for newborns, are needed to improve neonatal VD status.

Key words: 25-hydroxyvitamin D, Maternal supplementation, Newborn, Vitamin D deficiency, Vitamin D insufficiency

1. Introduction

Vitamin D (VD) deficiency and insufficiency during pregnancy is a serious health problem worldwide [1, 2]. Several studies have reported that VD insufficiency, indicated by serum 25-hydroxyvitamin D (25(OH)D) levels lower than 20 ng/mL [3], during pregnancy is associated with poor health outcomes in pregnant women and their newborns [4]. The effects of VD insufficiency in pregnant women include the increased risk of gestational diabetes mellitus, preeclampsia, caesarean section, and spontaneous abortion [1, 4-9]. Maternal VD insufficiency during pregnancy also affects newborns and causes low birth weight, preterm birth, and postnatal growth failure [2, 4-6]. In addition, maternal VD insufficiency during pregnancy is a risk factor for various morbidities in children after birth, including asthma, type 1 diabetes, multiple sclerosis, and autism [5].

VD status of pregnant women depends on dietary intake, geographic location, ultraviolet B exposure, ethnicity, and socioeconomic status. According to a previous systematic review, the frequency of VD insufficiency in pregnant women was 64%, 57%, and 46% in the United States, Europe, and Eastern Mediterranean countries, respectively, and was the highest (87%) in Southeast Asia [1]. In Japan, VD status of pregnant women is more serious. According to our previous study that used liquid chromatography-tandem mass spectrometry, almost all postpartum women showed VD insufficiency [10].

To prevent VD insufficiency during pregnancy, the global consensus group representing eleven international organizations recommended 600 IU/day of VD for all pregnant and lactating women to prevent osteomalacia in mothers and congenital rickets in newborns [3]. A previous

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report showed that 600 IU/day of VD supplementation could maintain 25(OH)D levels >20 ng/mL in more than 97.5% of pregnant and lactating women [11]. In Japan, no VD supplementation guideline exists, and no study has evaluated adequate VD intake in pregnant women. The Ministry of Health, Labour and Welfare recommends a VD intake of 340 IU/day in pregnant women [12], which is lower than the global standard. As VD status is influenced by dietary intake, lifestyle factors, and latitude, it is necessary to establish Japanese VD intake recommendation for pregnant women.

The most effective way to improve VD status is using dietary supplements [6]. A large number of pregnant women in Western countries take some form of commercial dietary supplements. In fact, approximately 80–90% of pregnant women in the United States and Europe consume commercial dietary supplements [13, 14]. In Japan, the number of pregnant women consuming commercial dietary supplements has increased in recent years, from approximately 20% in 2005 to 75% in 2010 [14, 15]. Although the number of commercial supplements containing VD alone is limited, most Japanese commercial supplements contain a certain amount of VD along with other nutrients, such as folic acid, calcium, and iron. To our knowledge, studies on evaluation of the effects of maternal supplement use during pregnancy are very limited in Japan, and most of them focused only on the effects of folic acid [14]. Additionally, no studies have examined the effects of VD-containing commercial supplements during pregnancy on VD status of mothers and newborns.

We hypothesized that the maternal use of VD-containing commercial supplements during pregnancy might improve VD status of newborns. This study aimed to examine the effects of maternal use of VD-containing commercial supplements on 25(OH)D levels in newborns.

2. Materials and Methods

2.1 Study population and data collection

This retrospective cohort study was performed at the Saitama City Hospital (35.9° North), located 25 km north of Tokyo. The participants were newborns registered in the Saitama City Hospital Infants Vitamin D Registry between August 2017 and July 2024. From this registry, we enrolled newborns born at ≥36 weeks of gestation in the Saitama City Hospital from January 2022 to December 2023, who required blood test at four days of age along with newborn screening tests. The main indication for blood tests was jaundice. Serum 25(OH)D levels were measured in the remaining samples after blood tests. Newborn twins were excluded from the study. Information about maternal supplement use during pregnancy was obtained through a questionnaire at one-month checkup. We asked mothers if they had consumed any commercial supplements during their pregnancy. If the answer was yes, we asked about the ingredients and duration of supplement intake. We excluded newborns whose mothers' answers to the questionnaire were insufficient to determine the exact duration and type of supplements taken, newborns whose mothers took supplements only during a part of pregnancy, and newborns whose mothers took supplements that did not contain VD. Newborns were then classified into supplement and non-supplement groups depending on maternal supplements use during pregnancy. In the supplement group, mothers regularly took VD-containing commercial supplements throughout pregnancy, whereas in the non-supplement group, mothers did not take any supplements during pregnancy. The estimated amount of maternal daily VD intake from the supplements was calculated based on the product information. Demographic health information and laboratory data, including maternal age, maternal use of infertility treatments, gestational age, and anthropometric measurements of newborns, were collected from electronic medical records. Based on a previous study [16], we evaluated serum alkaline phosphatase (ALP) and intact parathyroid hormone (iPTH) levels as bone metabolism markers. Serum ALP levels were assessed based on the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference method (IFCC method). An elevated ALP level was defined as ALP >560 IU/L, based on age-specific Japanese reference intervals [17]. An elevated iPTH level was defined as iPTH >65 pg/mL based on the reference range of the electrochemiluminescence immunoassay (ECLIA, Elecsys PTH, Roche Diagnostics).

2.2 Serum 25(OH)D measurement

We measured the serum 25(OH)D levels in the remaining blood samples by chemiluminescence immunoassay (CLIA) using the Liaison® 25 OH Vitamin D Total Assay with Precision and Liaison® XL Analyzer (DiaSorin Inc., MN, USA). The lower limit of quantification was 4 ng/mL. VD status was defined according to the serum 25(OH)D levels based on the international consensus as follows [3]: Serum 25(OH)D <20 ng/mL was defined as VD insufficiency, <12 ng/mL as VD deficiency, and >100 ng/mL as VD excess.

2.3 Statistical methods

Data are presented as the median (interquartile range [IQR]), except for sex and frequency of infertility treatment. We performed Wilcoxon tests to compare serum 25(OH)D levels between the supplement and non-supplement groups. In addition, Fisher's exact and *F*-tests were used to compare the frequencies of VD insufficiency/deficiency and variances in serum 25(OH)D levels between

the two groups, respectively. $p < 0.05$ was considered as statistically significant. All analyses were performed using the R version 4.4.0 for Mac.

2.4 Ethical approval

This study was conducted in accordance with the guidelines of the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Institutional Review Board Committee at the Saitama City Hospital (committee reference number: A2922). All participants were informed about the study and given an opportunity to opt out.

3. Results

3.1 Description of the study population

Patient selection is summarized in Fig. 1. During the study period, 650 newborns at four days of age required blood tests. Of these, 279 were eligible for inclusion in the study. We classified 103 newborns into the supplement group and 176 into the non-supplement group. Baseline clinical characteristics and laboratory data for both groups are presented in Table 1. No significant differences in background characteristics were observed between the supplement and non-supplement groups, other than maternal age and frequency of receiving infertility treatment. Mothers in the supplement group had higher maternal age ($p = 0.015$), higher frequency of receiving infertility treatment ($p < 0.001$), than those in the non-supplement group. Birth weight, birth length, and birth occipitofrontal circumference (OFC) did not differ significantly between the two groups. Two patients in the non-supplement group had hypocalcemia (Ca <8 mg/dL), whereas no patient with hypercalcemia (Ca ≥12 mg/dL) were observed in either group. None of the patients had elevated ALP levels, whereas two patients in the supplement group and six patients in the non-supplement group had elevated iPTH levels. The exact VD content of the maternal supplements was clear in 72 newborns. The median amount of VD intake from VD-containing commercial supplements was 280 IU/day. In these 72 newborns, serum 25(OH)D levels according to the VD content of the supplements showed that a higher VD content in maternal supplements did not necessarily correspond to higher 25(OH)D levels in newborns (Supplementary Fig. 1).

3.2 Comparison of VD status of newborns between two groups

The distribution of serum 25(OH)D levels in newborns in the supplement and non-supplement groups is shown in Fig. 2. All newborns had serum 25(OH)D levels above the lower limit of quantification (4 ng/mL). The serum 25(OH)D levels in newborns in the supplement group were higher than those in the non-supplement group (median [IQR]: supplement group 17.2 [14.6, 22.9] *vs.* non-supplement group 14.3 [11.6, 16.7]; $p < 0.001$). The frequency of VD insufficiency was lower in the supplement group than that in the non-supplement group (supplement group 69/103 (67.0%) *vs.* non-supplement group 158/176 (89.8%); $p < 0.001$). The frequency of VD deficiency in the supplement group was lower than that in the non-supplement group (supplement group 14/103 (13.6%) *vs.* non-supplement group 51/176 (29.0%); $p = 0.003$). In addition, the variances in serum 25(OH)D levels in the supplement group was significantly greater than that in the non-supplement group ($p < 0.001$). No newborns showed VD excess in either group, with the maximum serum 25(OH)D level recorded at 46.9 ng/mL.

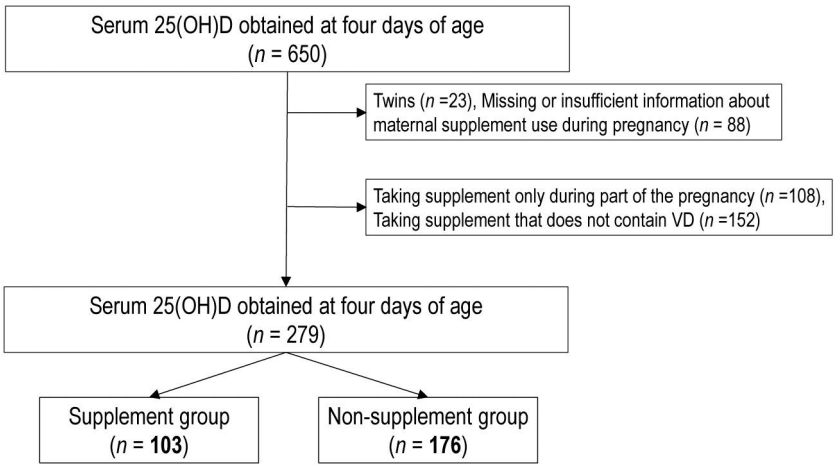


Fig. 1 Flow chart describing patient selection and classification
VD, vitamin D

Table 1 Baseline characteristics and laboratory data of the study subjects

	Supplement group (n = 103)		Non-supplement group (n = 176)	
Clinical characteristics	Median	IQR	Median	IQR
<Mothers>				
Age, years	34	30, 39	32	29, 36
Parity	0	0, 1	1.0	0, 1
Infertility treatment, *n* (%)	31 (30.1%)		15 (8.5%)	
<Newborns>				
Male, *n* (%)	53 (51.5%)		82 (46.6%)	
Gestational age, weeks	39 1/7	38 3/7, 40 1/7	38 5/7	38 1/7, 39 5/7
Birth weight, g	3,030	2,753, 3,290	2,953	2,719, 3,186
Birth length, cm	49.2	48.0, 50.3	48.5	47.3, 50.0
Birth OFC, cm	33.5	32.9, 34.0	33.5	32.5, 34.0
Laboratory data				
Serum 25(OH)D, ng/mL	17.2	14.6, 22.9	14.3	11.6, 16.7
Ca, mg/dL	9.7 (n = 58)	9.2, 10.0	9.4 (n = 99)	9.0, 9.7
Phosphate, mg/dL	6.9 (n = 57)	6.0, 7.6	6.7 (n = 99)	6.3, 7.2
ALP*, U/L	177 (n = 57)	157, 217	186 (n = 99)	156, 220
iPTH, pg/mL	32.0 (n = 21)	21.0, 36.0	41.0 (n = 37)	28.0, 58.0

Abbreviations: IQR, interquartile range; OFC, occipitofrontal circumference; ALP, alkaline phosphatase; iPTH, intact parathyroid hormone.
* Measured using the IFCC method.
No significant differences were found in the number of patients with serum calcium, phosphate, ALP, and iPTH levels between the supplement and non-supplement groups.

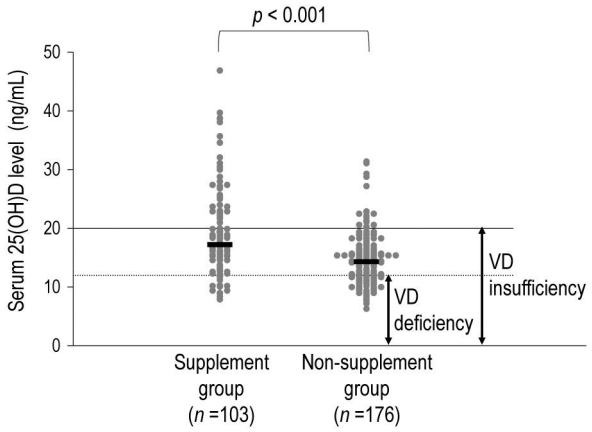
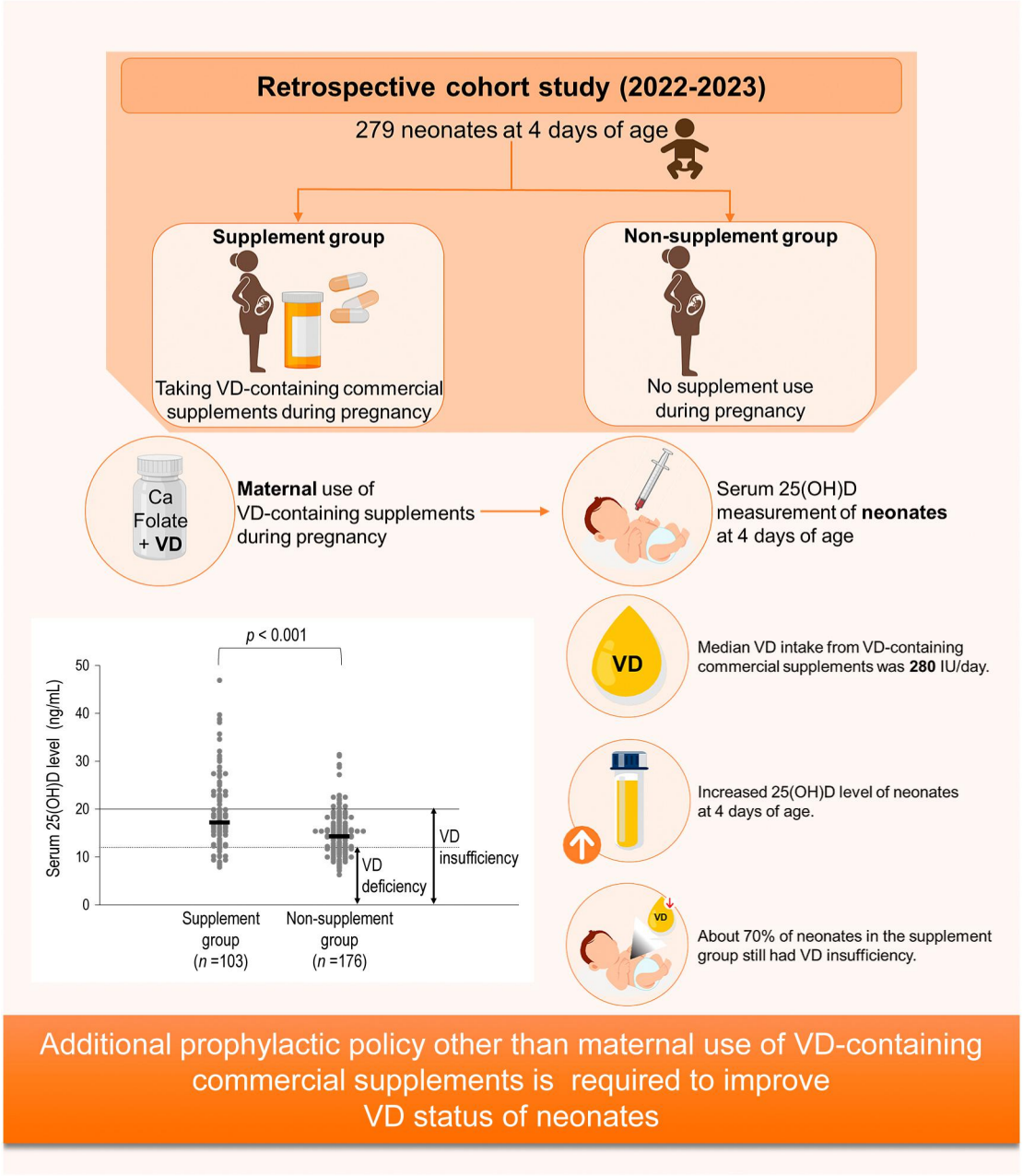


Fig. 2 The distribution of serum 25(OH)D levels in newborns in the supplement and non-supplement groups
Black bars indicate the median serum 25(OH)D levels in each group.VD, vitamin D.

4. Discussion

To the best of our knowledge, this is the first study to evaluate the effects of maternal use of VD-containing commercial supplements on VD status of newborns. Maternal use of VD-containing commercial supplements increased serum 25(OH)D levels in newborns, but it was inadequate to prevent VD insufficiency or deficiency in newborns (Graphical Abstract).

The baseline characteristics of the supplement and non-supplement groups showed that maternal age and frequency of receiving infertility treatment were higher in the supplement group than in the non-supplement group. This may reflect the fact that mothers in the supplement group had a high socioeconomic status and were more concerned about their health during pregnancy due to difficulties in having a baby and recommendation of a physician engaged in infertility treatment. Birth weight, birth length, and birth OFC were not significantly different between supplement and non-supplement groups, suggesting that maternal VD-containing supplements do not have a significant effect on newborn anthropometry or growth. Although two newborns in the non-supplement group showed hypocalcemia, these values were only slightly below the reference values, and we believe that the clinical impact of this result was not significant. No newborns had elevated ALP levels, suggesting that there were no cases of biochemical rickets at birth in the study population. Newborns with elevated iPTH levels were more frequently observed in the non-supplement group, suggesting that newborns in this group might have a higher risk of subclinical VD deficiency. The median amount of VD intake from commercial supplementations was 280 IU/day—less than half the globally recommended VD dose for pregnant women (600 IU/day).



Graphical Abstract

The amount of VD in Japanese commercial supplements is relatively low, resulting in inadequate maternal VD intake even among those using supplements consistently. Moreover, a higher VD content in maternal supplements did not necessarily correspond to higher 25(OH)D levels in newborns, reflecting the variability in adherence to supplement intake among mothers in the supplement group.

A comparison of the serum 25(OH)D levels in newborns between the supplement and non-supplement groups revealed several notable findings. First, the serum 25(OH)D levels in newborns in the supplement group were higher than those in the non-supplement group, with a median difference of 2.9 ng/mL. This result confirmed that regular use of VD-containing commercial supplements during pregnancy increased serum 25(OH)D levels in newborns, but the effect was limited. Second, the frequency of VD deficiency and insufficiency in the supplement group were lower than those in the non-supplement group, suggesting that maternal use of VD-containing supplements during pregnancy may improve VD status of newborns. However, because 67.0% of newborns in the supplement group still had VD insufficiency, maternal commercial supplementation alone was inadequate to prevent VD insufficiency in newborns. Consistent with this,

a previous study using cord blood reported that 90% of newborns showed VD insufficiency even when mothers received 4,200 IU/week of oral VD supplementation during pregnancy, the same dose as the global recommendation (600 IU/day) [18]. Indeed, the maternal use of VD supplements is effective in improving mothers' VD status; further measures are required to prevent VD insufficiency in newborns. Because the global consensus statement recommends 400 IU/day of VD for all infants from birth to 12 months of age [3], administering VD supplements to newborns is the most effective way to prevent neonatal VD insufficiency. Third, the variances in serum 25(OH)D levels evaluated using the *F*-test was significantly greater in the supplement group than that in the non-supplement group. This result reflects the variations in VD content in Japanese commercial supplements as well as variability in compliance with maternal supplement intake during pregnancy.

This study has certain limitations. First, because this was a single-center study, our results cannot be generalized to all newborns in Japan. Second, we were unable to evaluate maternal serum 25(OH)D levels. Third, mothers in the supplement group tended to have a higher socioeconomic status and greater health awareness. They may have been more attentive to their diet and sunlight exposure, which may have influenced the VD status of their newborns. Because the study period coincided with the COVID-19 pandemic, and pregnant women tended to refrain from going outside, we consider that the impact of sunlight exposure may have been minimal. Fourth, information on maternal supplement use was collected using questionnaires, which may have limited reliability. We confirmed that the supplements were continuously used during pregnancy; however, we did not specifically assess adherence during this period. Because supplements are not regulated as prescription medications, accurately verifying their intake details is difficult. Lastly, we could not assess clinical symptoms, such as craniotabes, and radiographic findings or bone density owing to the difficulty in performing these tests in newborns. Further studies are required to evaluate the effects of maternal VD supplementation on the clinical outcomes of newborns.

In conclusion, the maternal administration of VD-containing commercial supplements during pregnancy increased serum 25(OH)D levels in newborns at four days of age. However, approximately 70% of newborns showed VD insufficiency even after maternal supplementation. Additional measures, such as VD supplementation for newborns, are required to improve the neonatal VD status.

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Disclosure

The authors have no conflict of interest.

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Data Sharing

The data supporting the findings of this study are available on reasonable request from the corresponding author.

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