ORIGINAL

Seasonal variation of serum 25(OH) vitamin D levels in maternal and umbilical cord blood in Japanese women

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Abstract : We aimed to demonstrate that the serum 25-hydroxyvitamin D (25(OH)D) level in maternal and umbilical cord blood has a seasonal variation in Japanese women. The study cohort comprised 256 healthy Japanese women with a singleton pregnancy who delivered after 36 gestational weeks between 2012 and 2015. The season at delivery was categorized for 3 months and recorded as "spring", "summer", "autumn" and "winter". Subjects were divided into four groups according to season. A sample of peripheral venous blood at 35-36 gestational weeks and blood from the umbilical vein at delivery were taken. The mean serum 25(OH)D concentration (ng/mL) in maternal blood for each season (spring, summer, autumn and winter) was 18.0 (±6.7), 17.1 (±5.1), 21.6 (±8.0) and 16.0 (±5.1), whereas that for umbilical cord blood was 8.8 (±3.6), 8.6 (±2.6), 10.7 (±3.5) and 8.6 (±2.1), respectively. The mean serum 25(OH)D concentration of maternal and umbilical cord blood in autumn was higher than that for the other three seasons. In pregnant Japanese women, the mean serum 25(OH)D concentration in maternal and umbilical cord blood was affected by the season of delivery, with both being highest in autumn. Regardless of the season, the maternal serum concentration of 25(OH)D was low in Japan. J. Med. Invest. 66 : 128-133, February, 2019

Keywords : *25-hydroxyvitamin D, pregnancy, cord blood, season, vitamin D*

INTRODUCTION

Deficiency of vitamin D during pregnancy is a worldwide problem (1). Recent work has suggested that a low concentration of 25-hydroxyvitamin D (25(OH)D) in the mother is associated with complications such as preeclampsia, bacterial vaginosis, gestational diabetes mellitus (GDM), a small-for-gestational-age infant, and preterm birth (1-3). Furthermore, the 25(OH)D level in umbilical cord blood has been reported to be inversely associated with the risk of transient early wheezing and atopic dermatitis by the age of 5 years (4), and to be a predictor of neonatal total fat mass (5).

Several reports have shown maternal and umbilical-cord serum levels of 25(OH)D to be affected by season (5-7), because 25(OH)D production was dependent upon the action of sunlight on skin. Moreover, Day and colleagues stated that the season of birth was considered to be associated with birth weight, pubertal timing and height (8), and one of the reasons was considered to be maternal vitamin D status (VDS) during pregnancy. Therefore, maternal and fetal VDS according to season may be important not only for maternal/fetal health but also for future health. In addition, sunlight exposure is influenced by skin color, lifestyle, and geographic latitude. Consequently, the VDS of pregnant women of different geographic locations and skin colors has been reported.

However, despite the importance of VDS during pregnancy, the detailed seasonal variation of 25(OH)D levels in pregnant Japanese women has not been clarified. We aimed to demonstrate that the serum 25(OH)D level of maternal and umbilical cord blood has a seasonal variation, and to reveal the VDS in such women.

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MATERIALS AND METHODS

Study site

The study protocol was approved by the Ethics Committee of Tokushima University Graduate School (Tokushima, Japan). This prospective study was undertaken at Tokushima University Hospital (Tokushima, Japan), a tertiary perinatal care hospital located at latitude of 34° N in Japan. This location had an average ≈2121 h of daylight per year during this research period (9).

Study design

We evaluated 256 women with a normal singleton pregnancy who delivered at our hospital after 36 gestational weeks between 2012 and 2015. According to definitions set by the Japan Meteorological Agency, the season at delivery was categorized for 3 months and recorded as "spring" (March-April-May), "summer" (June-July-August), "autumn" (September-October-November) and "winter" (December-January-February). The subjects were divided into four groups using this category of seasons. All cases with threatened premature delivery, hypertensive disorders in pregnancy, gestational diabetes mellitus, maternal complications, hospitalized care in pregnancy, or use of corticosteroids or heparin were excluded from the study cohort. Maternal and neonatal parameters were obtained from the patients' medical records maintained by our hospital. These parameters were : maternal age at delivery ; parity ; height ; body weight before pregnancy and at delivery ; body mass index before pregnancy and at delivery ; gestational weeks of delivery ; season at delivery ; neonatal body weight ; length ; chest circumference ; head circumference ; Apgar score at 1 min ; Apgar score at 5 min ; pH of umbilical artery blood ; placental weight.

Biochemical analyses

For all eligible women, samples of maternal blood were collected at 35 or 36 gestational weeks and from the umbilical vein at delivery. The serum 25(OH)D concentration was measured using a radioimmunoassay kit (DiaSorin, Rome, Italy) which had a sensitivity of 5.0 ng/mL, inter-assay coefficient of variation of 4.9%, and intra-assay coefficient of variation of 5.5%.

Maternal vitamin D status

On the basis of the literature, we categorized a maternal serum 25(OH)D level ≥30 ng/mL as "sufficiency", 20-29.9 ng/mL as "insufficiency", ≤19.9 ng/mL as "deficiency" and ≤9.9 ng/mL as "severe deficiency" (1, 10, 11).

Statistical analyses

One-way factorial ANOVAs for continuous data and Fisher's exact tests were used to investigate the relationship between the season at delivery and selected data. After checking the normality of data distribution, we used the appropriate type of statistical analysis. Differences between each season were compared with Tukey's honestly significant difference test. The correlation between maternal serum 25(OH)D concentration and that of umbilical cord blood was evaluated using Pearson's correlation analysis. Differences between VDS and season were compared with Pearson's chi-square test. $P<0.05$ was considered significant. All statistical analyses were done using JMP v11 (SAS Institute, Cary, NC, USA).

RESULTS

The number of women who delivered during spring, summer, autumn and winter was 52, 75, 97 and 32, respectively. Their characteristics are summarized in Table 1. There were no significant differences in the backgrounds of these women or in neonatal outcomes.

The serum 25(OH)D concentration mean (±SD) in these 256 women was 18.8 (±7.0) ng/mL. The serum 25(OH)D concentration of women who delivered during spring, summer, autumn and winter was 18.0 (±6.7), 17.1 (±5.1), 21.6 (±8.0) and 16.0 (±5.1) ng/mL, respectively. The serum 25(OH)D concentration in the blood of women who delivered during autumn was significantly ($P<0.05$) higher than that in women who delivered during the other three seasons (Figure 1a).

In total, only 19 (7.4%) women were categorized as having a sufficient 25(OH)D concentration, and 61.3% had vitamin D deficiency or severe deficiency. Maternal VDS in each delivery season is shown in Table 2. These data showed that the prevalence of maternal vitamin D deficiency or severe deficiency was affected by season significantly ($P<0.001$). In autumn, the prevalence of vitamin D deficiency or severe deficiency was 42.3%, and was the lowest among the four seasons. In winter, 84.4% of women had vitamin D deficiency, and it was highest percentage among four seasons.

The mean 25(OH)D concentration in the serum of umbilical cord blood (ng/mL) was 9.4 (±3.3), and that in women who delivered during spring, summer, autumn and winter was 8.8 (±3.6), 8.6 (±2.6), 10.7 (±3.5) and 8.6 (±2.1), respectively. The mean 25(OH)D concentration in the serum of umbilical cord blood in women who delivered during autumn was significantly higher ($P<0.05$) than that in women who delivered during the other three seasons (Figure 1b).

The correlation between the serum 25(OH)D concentration of maternal blood and that of umbilical cord blood is shown in Figure 2. The 25(OH)D concentration in the serum of umbilical cord blood was strongly correlated with that of the mother ($r=0.72$, $P<0.001$).

Table 1 Baseline characteristics and outcomes of the 256 pregnant women.
Data are the mean ± SD or n (%).
BMI, body mass index.

	Total (n=256)	Spring (n=52)	Summer (n=75)	Autumn (n=97)	Winter (n=32)	*P*
Maternal characteristics						
Age at delivery (years)	32.9 (±5.2)	32.6 (±4.9)	32.4 (±5.6)	33.3 (±4.6)	33.6 (±5.9)	0.55
Height (cm)	158.4 (±5.1)	158.2 (±5.1)	158.3 (±4.7)	158.3 (±5.4)	159.1 (±5.3)	0.07
Body Weight at non-pregnant (kg)	52.5 (±8.4)	53.4 (±10.6)	52.8 (±8.0)	51.4 (±7.2)	53.6 (±8.8)	0.42
Body Weight at delivery (kg)	62.3 (±9.0)	64.1 (±10.2)	63.0 (±9.3)	60.4 (±7.4)	63.8 (±9.9)	0.05
BMI at Prepregnant (kg/m2)	20.9 (±3.1)	21.3 (±3.8)	21.0 (±2.9)	20.5 (±2.7)	21.1 (±3.6)	0.41
BMI at delivery (kg/m2)	24.8 (±3.3)	25.6 (±3.7)	25.1 (±3.4)	24.1 (±2.8)	25.1 (±3.8)	0.053
Primiparous (%)	139 (54.3)	31 (59.6)	39 (52)	52 (53.6)	17 (53.1)	0.85
Gestational age at delivery (weeks)	39.0 (±1.1)	39.1 (±1.1)	38.9 (±1.1)	39.0 (±1.1)	38.7 (±1.1)	0.31
Neonatal outcomes						
Birth weight (g)	3029 (±376)	3074 (±384)	3041 (±407)	3024 (±309)	2942 (±463)	0.47
Length (cm)	49.3 (±1.9)	49.2 (±1.8)	49.5 (±1.9)	49.5 (±1.7)	48.6 (±2.8)	0.12
Chest circumference (cm)	32.0 (±1.7)	32.2 (±1.4)	31.9 (±1.7)	32.2 (±1.6)	31.6 (±2.2)	0.23
Head circumference (cm)	33.4 (±1.3)	33.5 (±1.2)	33.2 (±1.3)	33.4 (±1.2)	33.3 (±1.4)	0.53
Apgar score at 1 min	8.1 (±1.2)	7.8 (±0.2)	8.1 (±0.1)	8.1 (±0.1)	8.3 (±0.2)	0.46
Apgar score at 5 min	9.1 (±1.0)	9.0 (±1.5)	9.1 (±1.2)	9.2 (±0.5)	9.0 (±0.9)	0.69
pH of umbilical artery blood	7.26 (±0.46)	7.29 (±0.06)	7.29 (±0.07)	7.21 (±0.74)	7.31 (±0.06)	0.63
Placental weight (g)	562.5 (±299.8)	555.5 (±98.5)	596.7 (±524.1)	547.2 (±132.1)	540.7 (±115.0)	0.71

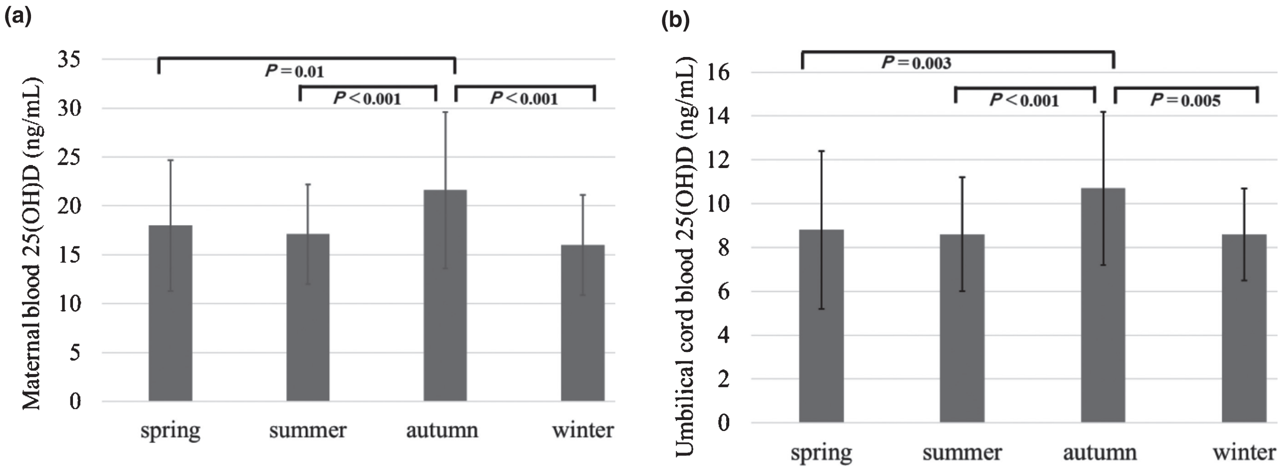

Figure 1 Mean serum (25(OH)D) concentration according to the season at which delivery occurred.
(a) Maternal blood.
(b) Umbilical cord blood.

Table 2 Vitamin D status of 256 pregnant Japanese women

Vitamin D Cutoff	Suffciency		Insuffciency		Deficiency		Severe deficiency	
	≥30ng/mL		20-29.9ng/mL		10-19.9ng/mL		<10ng/mL	
	n	%	n	%	n	%	n	%
Spring(n=52)	2	3.8	17	32.7	31	59.6	2	3.8
Summer(n=75)	1	1.3	18	24	53	70.7	3	4
Autumn(n=97)	15	15.5	41	42.3	39	40.2	2	2.1
Winter(n=32)	1	3.1	4	12.5	27	84.4	0	0
Total(n=256)	19	7.4	80	31.3	150	58.6	7	2.7

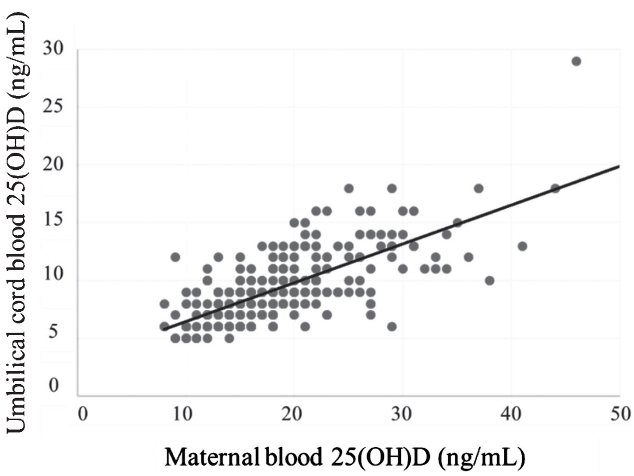

Figure 2 The correlation between the serum 25(OH)D concentration of maternal blood and that of umbilical cord blood.

DISCUSSION

Our study yielded two important clinical observations. First, the serum 25(OH)D concentration in both maternal and umbilical cord blood had a seasonal variation in Japanese women with a singleton pregnancy. The serum 25(OH)D concentration in both maternal and umbilical cord blood of women who delivered in autumn was significantly higher than that in other seasons. Second, regardless of the season, the maternal serum concentration of 25(OH)D was low, and the proportion of vitamin D deficiency or severe deficiency was high.

First, we found that the serum 25(OH)D levels in maternal and umbilical cord blood showed a seasonal variation in pregnant Japanese women. Moreover, maternal VDS was affected by season. Studies from Germany (12), Greece (13), Norway (5) and Poland (7) have shown a tendency for a higher concentration of vitamin D among pregnant women during summer because of greater sun exposure than in other seasons. In addition, winter has been reported to be a risk factor for vitamin D deficiency in pregnant women in Korea (14). In our study, the serum 25(OH)D concentration at 35 or 36 gestational weeks in pregnant women who delivered in autumn was significantly higher than that in other seasons, and there was no significant difference between the other seasons. During the period of our study, the Mean Ultraviolet Index (UVI ; an international standard measurement of the strength of sunburn-producing UV radiation at a particular place and time) in summer at Tokushima was >6, whereas the mean UVI was <6 in the other three seasons (9). Therefore, greater sun exposure in third trimester was considered to increase the maternal serum 25(OH)D concentration in the autumn group. Seasonality of maternal complications such as GDM and hypertensive disorders of pregnancy have been reported (15-18), and may be related to maternal VDS. Then, the serum 25(OH)D concentration in umbilical cord blood in autumn was also the highest among the four seasons. This result showed the same tendency as maternal data. The reason for this tendency was a strong correlation between the serum 25(OH)D concentration in maternal and umbilical cord blood. This correlation has been documented outside Japan (5, 18-20), and we have shown this to be the case in Japanese women too. There were no significant differences in the neonatal outcomes. However, the 25(OH)D level in umbilical cord blood has been reported to be a childhood event (4, 5). Seasonal variation in the serum 25(OH)D concentration of umbilical cord blood may make a difference to future health. Day and colleagues reported that the season of birth was associated with birth weight, pubertal timing and height, and one of the reasons was considered to be exposure to vitamin D in the uterus (8). Therefore, the season of birth may affect the future health of the infant in Japan as well.

Second, in the light of current recommendations, the serum 25(OH)D concentration in maternal blood should be ≥30 ng/mL (22, 23). However, we showed that the mean serum 25(OH)D concentration in maternal blood was classified as deficient or severe deficient in 61.3% of cases, and was deemed sufficient in only 7.4% of participants. In winter, 84.4% of pregnant women had vitamin D deficiency. Even in autumn (when the highest level was noted), the mean maternal serum 25(OH)D concentration was insufficient, and 42.3% of women had vitamin D deficiency or severe deficiency.

Vitamin D deficiency in pregnant women has been reported worldwide (1). In the United States, vitamin D deficiency is estimated to occur in 5-50% of pregnant women (19, 24). In Korea and Poland, studies have shown the overall prevalence of vitamin D deficiency in pregnant women to be 77.3% and 50.0%, respectively (7, 14). In Japan, scholars have shown that 58.5% of participants had severe vitamin D deficiency and 95.4% of participants had vitamin D deficiency (25). Our data showed the same trend as that in other countries and confirmed the lack of vitamin D in pregnant Japanese women. Low levels of 25(OH)D in infants increases the risk of skeletal diseases such as rickets and hypocalcemia. Hence, vitamin D deficiency may affect not only complications during pregnancy, but also the development of children, and appropriate measures are necessary.

In terms of prevention of vitamin D deficiency, supplementation seems to be useful. Several reports have shown that vitamin D supplementation increases vitamin D levels in pregnant women deficient in vitamin D (26-28). However, the importance of vitamin D levels for pregnant women is not well known in Japan, so we hypothesize that few pregnant women would have taken vitamin D supplements in the present study. However, current evidence suggests unclear benefits of routine supplementation of vitamin D for maternal/child health outcomes (29). Furthermore, the optimal dose of vitamin D supplementation during pregnancy is controversial. According to recommendations in guidelines from Scandinavian countries and the United Kingdom, all pregnant women should take 10 μg (400 IU) of vitamin D every day (30-32). Guidelines from the World Health Organization (33), Institute of Medicine (34), Endocrine Society (35) and Canadian Pediatric Society (36) differ. Moreover, there is no consensus on the optimal maternal serum concentration of 25(OH)D. Further study is necessary to ascertain the optimal dose of vitamin D supplementation and optimal maternal serum concentration of 25(OH)D.

Abbreviations : confidence intervals, CI

The fetus is dependent entirely on the supply of 25(OH)D from the mother. 25(OH)D can pass through the placenta and is activated to 1,25$(OH)_2D$ by fetal kidneys, but 1,25$(OH)_2D$ does not pass through the placenta (37). In addition, 25(OH)D is inactivated to 24, 25$(OH)_2D$ by 24-hydroxylation in the placenta (37). The role of placental metabolism compared with bone metabolism in the fetus has not been clarified, but it is thought to maintain rapid development of bone in the fetus in late pregnancy. In the fetal period, calcium and phosphorus supplied from the mother has a greater effect on bone metabolism than 25(OH)D. However, some reports have demonstrated maternal 25(OH)D status to be associated with the bone mass of their children later in life (38, 39). After birth, 25(OH)D regulates absorption of calcium and phosphorus from the intestine, and has an important role in bone metabolism. The mother must be informed that sunbathing is an important factor when breastfeeding infants because the main source of 25(OH)D is dietary intake and sunlight exposure. Besides supplementation with vitamin D, the mother must be informed that the 25(OH)D concentration in maternal blood and umbilical cord blood has seasonal variations.

Our study had three main limitations. First, we did not investigate factors considered to affect the serum 25(OH)D concentration in participants, such as diet, intake of supplements, regular use of sunscreen, and sunlight exposure. Second, study participants lived in Tokushima, so this research may not be generalizable to the VDS of all pregnant Japanese women because sunshine duration and latitude vary in different parts of Japan. Third, our study was relatively small and retrospective.

Further studies using a larger study cohort and prospective study design are needed.

CONCLUSIONS

Our data revealed that the serum 25(OH)D concentration of maternal and umbilical cord blood had a seasonal variation, with higher levels in autumn than in the other three seasons, in pregnant Japanese women. The mean serum 25(OH)D concentration in maternal blood was insufficient in all seasons, even in autumn (when the highest concentration was registered). The present study will serve as a foundation for future investigations on adequate supplementation of vitamin D for pregnant Japanese women.

CONFLICT OF INTEREST

The authors have no finan

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