Effect of prolonged hospitalization for threatened preterm labor on maternal and fetal vitamin D levels

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A short running title:
Maternal hospitalization and vitamin D

Abstract

Aim: We aimed to evaluate the effect of prolonged hospitalization for threatened preterm labor on maternal and fetal vitamin D status.

Methods: This was a retrospective cohort study, spanning 4 years, including 18 women with threatened preterm labor and 36 women with normal pregnancy, who received prenatal care for a singleton pregnancy at our center. Threatened preterm labor cases were women who were admitted to our hospital after the second trimester test, for at least 28 days, during which, the third trimester test was also performed. Controls were randomly sampled from women matched for age as well as the season during which the third trimester test was performed. Serum 25-hydroxyvitamin D concentration in maternal blood was compared between the two groups at second trimester, third trimester and in the umbilical cord blood at delivery.

Results: The mean±SD of maternal serum 25-hydroxyvitamin D concentration in the threatened preterm labor group (14.0±3.0 ng/mL) was significantly lower than that in the control group (17.8±5.9 ng/mL) (p<0.01) in the third trimester, although there was no significant difference in the second trimester (p=0.30). There was a significant reduction (p<0.01) in the maternal serum 25-hydroxyvitamin D from the second to third trimester, in the threatened preterm labor group, compared to the control group (p=0.60). There was no significant difference between the two groups in umbilical cord blood 25-hydroxyvitamin D concentrations at delivery (p=0.41).

Conclusions: Prolonged hospitalization for threatened preterm labor reduced the maternal vitamin D status, but did not influence the neonatal status at delivery.

Keywords

Nutrition, Premature Delivery

Introduction

Maternal vitamin D insufficiency during pregnancy is a common public health problem worldwide.[1, 2] Many previous studies have reported that deficiency of serum 25-hydroxyvitamin D (25(OH)D) during pregnancy, which is considered to accurately reflect vitamin D stores in the body, was significantly associated with various adverse perinatal outcomes, including preeclampsia,[3-6] gestational diabetes mellitus,[7] low neonatal birthweight,[8, 9] and others.[10, 11]

Exposure to ultraviolet sunlight affects the serum 25(OH)D concentration, since vitamin D is produced in the skin from ultraviolet energy.[12] Prolonged hospitalization for threatened preterm labor is thought to decrease the serum 25(OH)D concentration, due to prolonged interruption in exposure to ultraviolet sunlight. However, only a few studies have suggested an association between threatened preterm labor and maternal vitamin D insufficiency[13,14]; no studies have reported a direct correlation in the decrease of serum 25(OH)D concentration due to prolonged hospitalization during pregnancy.

The objective of this study was to demonstrate the effect of prolonged hospitalization for threatened preterm labor on maternal and fetal vitamin D levels.

Methods

This retrospective study was conducted in a cohort of women with singleton pregnancies, who received prenatal care and delivered after 36 weeks of gestation at a single perinatal care center in Japan, between 2012 and 2015. All patients underwent investigations for routine prenatal blood screening at 10-12 weeks, 24-26 weeks, and 35-36 weeks of gestation, as first trimester, second trimester, and third trimester tests respectively. All cases with hypertensive disorders in pregnancy, diabetes mellitus, gestational diabetes mellitus, maternal complications requiring medication, prenatally diagnosed fetal malformations, and women who were on heparin therapy were excluded from the study cohort.

Cases between 22 and 34 weeks of gestation with regular objective uterine contractions and/or significant cervical changes (dilatation and/or effacement) were diagnosed as threatened preterm labor (TPL) and were recommended hospitalization by trained obstetricians. Tocolytic agents were administered to all TPL admitted women, to reduce uterine contractions and prolong the pregnancy. Intravenous ritodrine hydrochloride was administered as a first-line tocolytic agent, and the dose was adjusted as required, based on the symptoms of preterm labor. Magnesium sulfate was used as a second-line tocolytic agent for women who continued to have symptomatic uterine contractions, after the highest-dose of ritodrine hydrochloride and to women, who were not administered ritodrine hydrochloride due to adverse effects. Antenatal corticosteroids were also administered when delivery at <34 weeks of gestation was expected. All TPL admitted women were instructed to walk only inside

the ward. Meals in the hospital included 626 milligrams of calcium, 1145 milligrams of phosphorus, 7 micrograms of vitamin D, and 2000 kilocalories per day on an average. At 35-36 weeks of gestation, doses of all other tocolytic agents were reduced and they were discontinued after the third trimester test. All women who had no signs of onset of labor were discharged a few days later.

Cases were recruited from women who were admitted with TPL after the second trimester test, and were hospitalized for at least 28 days until the third trimester test (Figure 1). All women who were administered magnesium sulfate as a tocolytic agent and/or antenatal corticosteroids were excluded from the study. We randomly recruited twice the number of cases who did not undergo hospitalization, as controls. They were matched for maternal age (±1 age) as well as the seasonal calendar quarter during which third trimester test was performed. The seasonal calendar quarters were defined as: spring (March, April, and May), summer (June, July, and August), autumn (September, October, and November), and winter (December, January, and February). The study was approved by our institutional review board.

Serum 25(OH)D concentration was measured with a radioimmunoassay kit (DiaSorin Ltd., Boldon, UK), which has a sensitivity of 5.0 ng/mL and inter- and intra-assay coefficients of variability of 4.9% and 5.5%, respectively. Serum calcium and phosphorus concentration were measured using an automatic analyzer (Olympus AU 5431, Tokyo, Japan). Corrected serum calcium was arrived at, based on serum albumin levels. These tests were conducted using the residual sera from routine prenatal blood screening at the second trimester, third trimester, and umbilical cord blood tests at delivery.

The following maternal parameters were documented: age at delivery, parity, height, body mass index both before pregnancy and at delivery, history of smoking or alcohol during pregnancy, seasonal calendar quarter at the third trimester test. Neonatal parameters documented were gestational age at birth, birthweight, length, head circumference, Apgar score at 1 minute and 5 minutes after birth, and umbilical arterial gas analysis. For TPL mothers, gestational age at admission during the second trimester, days between admission and third trimester test, tocolytic agents administered, days between third trimester test and delivery, days between discharge and delivery were also recorded.

Demographic data of TPL and control groups was compared using *t* tests for continuous data and Fisher's exact tests for categorical data. The maternal serum concentrations of 25(OH)D, calcium, and phosphorus were also compared between the two groups using *t* tests, at the second and third trimester. Maternal serum 25(OH)D concentration in the third trimester was compared to the concentration during second trimester using paired-*t* tests, for each group. Additionally, the serum concentration of 25(OH)D, calcium, and phosphorus in the umbilical cord blood at delivery were also compared between two groups using *t* tests. Values of $p<0.05$ were considered as statistically significant. All statistical analyses were performed using JMP software (JMP version 11; SAS Institute Inc., Cary, NC, USA).

Results

Eighteen women with prolonged hospitalization and 36 matched control subjects were enrolled in this study. The maternal baseline characteristics and pregnancy outcomes are summarized in Table 1. The percentage of cases in which the third trimester tests were conducted during spring, summer, autumn, and winter were 11.1%, 22.2%, 44.4%, and 22.2%, respectively. There were no significant differences between the two groups in baseline maternal pregnancy characteristics. The duration of pregnancy in TPL group (37.9±1.5 weeks) was significantly shorter than that in control group (39.2±1.2 weeks) (p<0.01) and neonatal body weight in TPL group (2811.2±365.5 grams) was significantly lower than that in control group (3071.4±283.1 grams) (p=0.02). Hospitalization data of the TPL group is shown in Table 2. The mean±SD period of gestation at admission was 27.6±2.3 weeks. The mean±SD of the days from admission to the third trimester test was 52.8±15.7 days.

Table 3 shows the comparison of maternal 25(OH)D, albumin-corrected calcium and phosphorus concentration between the TPL and control groups. In the second trimester, the mean±SD of maternal serum 25(OH)D concentrations in TPL group was 19.2±6.3 ng/mL and that in the control group was 17.4±6.0 ng/mL. There was no significant difference between the two groups (p=0.30). On the other hand, in the third trimester, the mean±SD of maternal serum 25(OH)D concentration in TPL group (14.0±3.0 ng/mL) was significantly lower than that in control group (17.8±5.9 ng/mL) (p<0.01). There were no significant differences between the two groups in maternal albumin, corrected calcium, as well as phosphorus concentration.

Figure 2 shows the changes in maternal serum 25(OH)D concentration from the second to third trimester in both groups. Although maternal serum 25(OH)D concentration in the control group did not significantly change from the second to third trimester (p=0.60), there was significant reduction (p<0.01) in 25(OH)D concentration in the TPL group in the same period.

The comparison of 25(OH)D, albumin-corrected calcium and phosphorus concentrations in the umbilical cord blood at delivery between the two groups is shown in Table 4. The mean±SD of umbilical cord 25(OH)D concentrations in the TPL group was 8.6±1.8 ng/mL and that in the control group was 9.0±2.1 ng/mL. There were no significant differences between the two groups for any of the three blood concentrations.

Discussion

This study had two significant findings. The first was that, prolonged hospitalization for TPL during pregnancy leads to a decrease in maternal vitamin D levels. The second finding was that this reduction in maternal vitamin D, did not necessarily affect the fetal vitamin D levels at delivery.

Changes in maternal serum 25(OH)D concentration during pregnancy are considered to vary

based on the season, because ultraviolet sunlight exposure varies with the season. In our control group, the maternal serum 25(OH)D concentration revealed no significant changes from the second to third trimester. On the other hand, in the TPL group, which included women matched to controls for the season, the maternal 25(OH)D concentration significantly decreased during the same period. On comparing the two groups, it was seen that maternal serum 25(OH)D concentration in the TPL group was significantly lower than that in the control during the third trimester, although there was no significant difference between the groups in 25(OH)D concentration, in the second trimester. We presume that hospitalization deprived the mothers of ultraviolet sunlight, which they are exposed to in everyday life and that a prolonged deprivation caused reduction of the serum 25 (OH)D concentration. Several previous studies have reported that prolonged bed rest affected bone metabolism in both, pregnant and non-pregnant women.[15-18] Similarly in our study, bed rest due to prolonged hospitalization might have affected the maternal vitamin D levels.

Several authors have described the correlation between vitamin D insufficiency and TPL in previous studies. Shibata et al.[14] reported that serum 25(OH)D concentrations in women with TPL were lower than that in women with normal pregnancy at 30 weeks of gestation; however, the effect of hospitalization in this study was not clear. Nishimura et al[13] reported that serum 25(OH)D concentrations in women with TPL were lower than concentrations in the control group after hospitalization for more than a month. However, in this study, there were only 5 cases of hospitalization, which included women with twin and triplet pregnancies. Bone metabolism including calcium and vitamin D status in multiple pregnancy has been reported to be different than that in singleton pregnancy, in several previous studies.[10, 19-21] Moreover, the effect of hospitalization was not clear because there were no comparable pre-hospitalization data. The serum half-life of 25(OH)D has been reported to be approximately 15 days.[22] Kaji et al[15] reported that hospitalization for a month or more during pregnancy changed several bone turnover markers. To our knowledge, our study is the first to confirm that prolonged hospitalization of more than 28 days for TPL, decreased maternal serum 25(OH)D concentrations compared to pre-hospitalization, in singleton pregnancies.

Our study also revealed that there were no significant differences in 25(OH)D concentrations in the umbilical cord blood between the two groups, although the maternal serum 25(OH)D concentration in women with prolonged hospitalization was significantly lower during the third trimester. Many previous reports have demonstrated a positive correlation between the 25(OH)D concentration in maternal blood, and that in the umbilical cord blood at delivery.[23-26] The reason for discrepancy between the maternal and the umbilical cord 25(OH)D concentrations in our study was not completely clear; however, we presume that the decreased 25(OH)D concentration in the TPL group had recovered due to ultraviolet sunlight exposure after discharge, until delivery. In fact, an additional analysis demonstrated that there was a significant positive correlation between the duration from hospital discharge to delivery and the ratio of the 25(OH)D concentration in the umbilical cord blood to that in maternal third trimester blood in the TPL group ($r=0.56$, $p=0.03$).

The decrease in maternal vitamin D levels due to prolonged hospitalization might not always

affect the neonatal vitamin D status at delivery. However, the maternal 25(OH)D reduction is an important concern. Maternal vitamin D deficiency has been reported to be significantly associated with adverse outcomes in neonates or early childhood, in several previous studies.[2,11] Maternal vitamin D insufficiency from prolonged hospitalization might irreversibly affect the fetal bone metabolism, although the levels might have recovered after discharge. Recently, Rodda et al.[27] demonstrated that supplementation of vitamin D in women with low vitamin D concentration during pregnancy, increased 25(OH)D concentration in the umbilical cord blood at delivery. However, it has not been confirmed whether maternal vitamin D supplementation during pregnancy, improves the short-term and long-term neonatal outcomes, and who are the pregnant women that require vitamin D supplementation. Our study revealed that women with prolonged hospitalization for TPL might be candidates for vitamin D supplementation, but this is a challenge for the future.

Several limitations of this study need to be acknowledged. First, there was no data about vitamin D supplementation in the control group. A few women in the control group might have been taking vitamin D supplementation and this could have increased their vitamin D levels, although no women took vitamin D supplementation during hospitalization in the TPL group. However, the importance of vitamin D levels during pregnancy is not well known in Japan, so we assume that few pregnant women would have taken vitamin D supplements. Second, tocolytic agents might have affected the maternal vitamin D status in TPL group. Intravenous ritodrine hydrochloride was administered for long periods to all cases in TPL group. The effect on bone metabolism and vitamin D status of this agent is not clearly understood. Recently, a few studies have suggested an association between prolonged magnesium administration and maternal and/or neonatal bone metabolism;[28,29] hence, women who were administered magnesium sulfate were excluded from our study population. Third, there were no data of any biochemical substances, which can affect vitamin D kinetics except for calcium and phosphorus, e.g., parathyroid hormone or vitamin D binding protein. These serum concentrations might affect the change in 25(OH)D during hospitalization and might help us to understand their effect on bone metabolism.

In conclusion, our study demonstrated that prolonged hospitalization during pregnancy reduced the maternal vitamin D levels. This reduction did not necessarily affect the neonatal vitamin D status at delivery. At present, it remains unclear whether maternal vitamin D insufficiency during hospitalization is associated with adverse outcomes of the neonate and whether vitamin D supplementation can improve the outcomes.

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Disclosure

The authors have no financial interests to declare in relation to the content of this article.

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Figure 1

A schematic diagram, showing the course of pregnancy in women recruited for the study. Women in threatened preterm labor group were admitted to the hospital after the second trimester test, remained in hospital for at least 28 days, and underwent the third trimester test during hospitalization (a). Women in the control group did not undergo hospitalization before delivery (b).

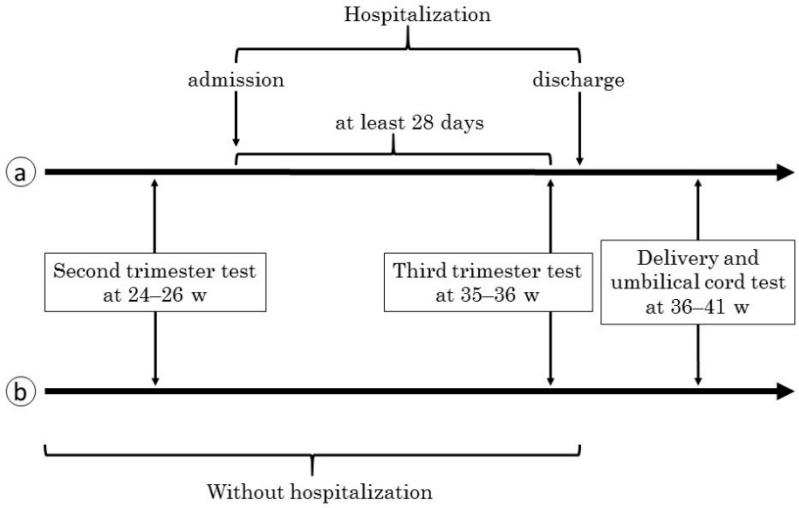

Figure 2

Changes in maternal serum 25-hydroxyvitamin D (25(OH)D) concentration of the study population from second trimester to the third trimester.

(a) Threatened preterm labor group

(b) Control group

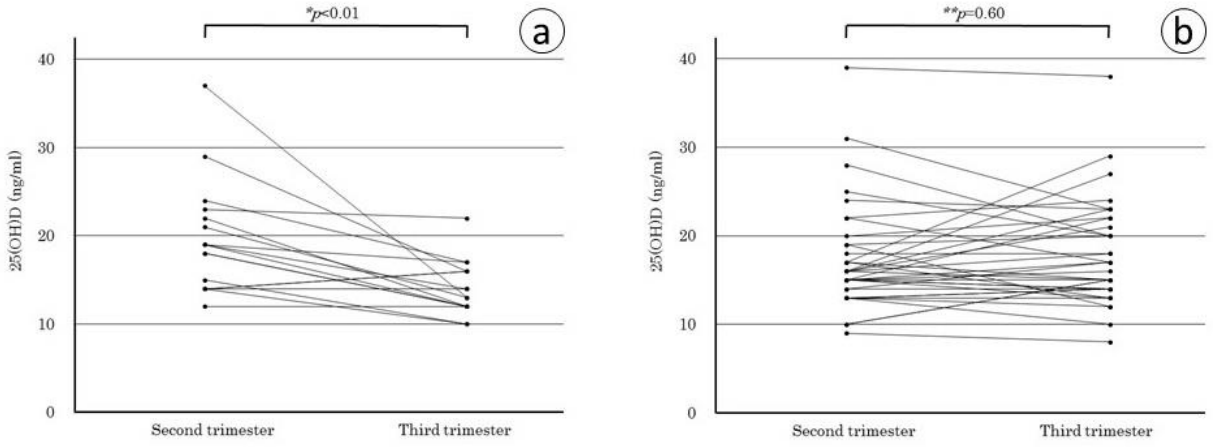

Table 1

Baseline characteristics and outcomes of patients in the study

Variables	TPL group (n=18)	Control group (n=36)	*P*
Maternal characteristics			
Age at delivery (years)	31.4±6.0	31.5±5.7	0.93
Nulliparous	9 (50)	23 (63.9)	0.39
Body height (cm)	156.8±6.4	157.9±4.7	0.45
BMI before pregnancy (kg/m^2)	20.2±0.9	22.1±0.6	0.08
History of smoking	1 (5.6)	0 (0)	0.33
History of alcohol consumption	0 (0)	0 (0)	*
Seasonal calendar quarter during the third trimester test			*
Spring	2 (11.1)	4 (11.1)	
Summer	4 (22.2)	8 (22.2)	
Autumn	8 (44.4)	16 (44.4)	
Winter	4 (22.2)	8 (22.2)	
Labor outcome			
Gestational age (weeks)	37.9±1.5	39.2±1.2	<0.01
BMI at delivery (kg/m^2)	23.5±2.1	25.8±4.0	0.02
Body weight gain during pregnancy	8.2±4.1	9.8±3.7	0.09
Neonatal outcomes			
Birth weight (grams)	2811.2±365.5	3071.4±283.1	<0.01
Length (cm)	49.1±2.5	49.7±1.3	0.26
Head circumference (cm)	33.7±1.3	33.1±1.2	0.12
Apgar score at 1 min	8.0±0.7	8.2±1.6	0.69
Apgar score at 5 min	9.1±0.6	9.2±0.4	0.36
pH of umbilical cord artery blood	7.28±0.06	7.30±0.06	0.12

Data are presented as mean±SD or *n* (%). BMI, body mass index; TPL, threatened preterm labor

Table 2

Hospitalization data of threatened preterm labor group in the 18 women

Variables	mean±SD or *n* (%)
Gestational age on admission (weeks)	27.6±2.3
Duration of hospitalization to third trimester test (days)	52.8±15.7
28–30	1 (5.6)
31–40	3 (16.7)
41–50	2 (11.1)
51–60	8 (44.4)
61–70	2 (11.1)
71–80	0 (0)
81–90	2 (11.1)

Table 3

Comparison of maternal 25-hydroxyvitamin D, albumin-corrected calcium and phosphorus concentration between the two groups

Variables		TPL group	Control group	*P*
Second trimester	25(OH)D (ng/mL)	19.2±6.3	17.4±6.0	0.30
	Calcium (mg/dL)	9.2±0.2	9.3±0.2	0.34
	Phosphorus (mg/dL)	3.4±0.5	3.5±0.4	0.27
Third trimester	25(OH)D (ng/mL)	14.0±3.0	17.8±5.9	0.01
	Calcium (mg/dL)	9.5±0.2	9.5±0.3	0.29
	Phosphorus (mg/dL)	4.1±0.5	3.9±0.8	0.50

Data are presented as mean±SD. TPL, threatened preterm labor; 25(OH)D, 25-hydroxyvitamin D

Table 4

Comparison of umbilical cord 25-hydroxyvitamin D, albumin-corrected calcium and phosphorus concentration between the two groups

Variables	TPL group	Control group	*P*
25(OH)D (ng/mL)	8.6±1.8	9.0±2.1	0.41
Calcium (mg/dL)	10.4±0.5	10.3±0.9	0.57
Phosphorus (mg/dL)	7.0±3.6	6.7±3.9	0.81

Data are presented as mean±SD. TPL, threatened preterm labor; 25(OH)D, 25-hydroxyvitamin D