# The association of 25-hydroxy Vitamin D level in mothers with term and preterm delivery and their neonates

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**Background:** Risk factors for maternal Vitamin D deficiency and preterm birth are convergence, but the distribution of 25-hydroxyvitamin D (25(OH) Vitamin D) levels among preterm infants is not known. We aimed to assess the association of 25(OH) Vitamin D levels in mothers with term and preterm delivery with their neonates. **Materials and Methods:** This case–control study was conducted on 62 mothers with spontaneous preterm delivery and their neonates as the case group and 124 mothers with term delivery and their neonates as the control group. From mothers and neonate's umbilical cord at birth, 10 cc blood was taken and immediately sent to the laboratory for measuring Vitamin D levels . Pearson correlation, independent samples $t$-test, and kappa concordance coefficient were used for data analysis. **Results:** In the term group, 102 cases (82.3%) had Vitamin D deficiency/insufficiency and 22 cases (17.7%) had normal Vitamin D level while in the preterm group, 56 cases (90.3%) had Vitamin D deficiency/insufficiency, and 6 cases (9.7%) had normal Vitamin D level ($P > 0.05$). The correlation between maternal and neonatal 25(OH) Vitamin D levels in the term and preterm group was statistically significant (term group: $r = 0.874$, $P < 0.001$ and preterm group: $r = 0.733$, $P < 0.001$). **Conclusion:** Our study did not show a significant difference between two groups in terms of Vitamin D status both in mothers and neonates while the significant association was found between Vitamin D levels of mothers and neonates in both groups. These findings confirmed the previous studies' findings that Vitamin D levels in neonates could be predicted from their mothers. As a result, successful Vitamin D and calcium supplementation for improving 25(OH) Vitamin D levels in the maternal and neonatal populations for protecting the harmful effects of Vitamin D insufficiency/deficiency are recommended.

**Key words:** 25-hydroxy Vitamin D, neonates, spontaneous preterm delivery, term delivery

## INTRODUCTION

Preterm birth is the world's leading cause of death in children under 5 years.[1] It has been estimated that 11% of all yearly deliveries in the world are preterm and 1 million out of 6 million newborn premature die from complications of prematurity; up to 27% of all deliveries in low- and middle-income countries are preterm and small gestational for age.[2] Preterm and small gestational for age births are associated with adverse health outcomes such as increased neonatal and infant mortality, childhood nutritional and visual and hearing impairments, and adulthood metabolic disease .[3,4] Risk factors for preterm birth include African–American race, poverty, young maternal age, obesity, as well as Vitamin D deficiency.[5] Vitamin D status in the fetus and newborn infant is largely determined by maternal Vitamin D status.[6] Because maternal Vitamin D insufficiency is common, it is likely that many newborns are also at high risk of insufficiency and deficiency of 25-hydroxy vitamin D (25(OH) Vitamin D) levels. Investigators have recently demonstrated an adverse role of low Vitamin D levels on health conditions beyond the traditionally

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understood calcium metabolism and bone health, such as health status throughout pregnancy[7] and during infancy and childhood.[8] Low maternal 25(OH) Vitamin D concentrations during pregnancy also have been shown to be associated with increased risks of specific conditions, including gestational diabetes, preeclampsia, and poor fetal growth, bacterial vaginosis, asthma, and schizophrenia.[9-13]

Because fetal growth restriction is associated with perinatal morbidity and mortality and later-life chronic disease, it is imperative to find modifiable risk factors for this adverse birth outcome. Risk factors for maternal Vitamin D deficiency and preterm birth overlap, but the association between levels of 25(OH) Vitamin D in mothers and their neonates has been investigated rarely particularly both among term and preterm delivery.

In this study, our primary hypothesis is to evaluate the association of 25(OH) Vitamin D levels in mothers with term and preterm delivery with their neonates. The secondary objective of the current study was to compare the 25(OH) Vitamin D levels in mothers with term and preterm delivery.

## MATERIALS AND METHODS

### Study design and participants
This case–control study was approved by Ethics Committee of Isfahan University of Medical Sciences (study's project number 293132). The sample size was determined based type one error rate 5%, statistical power 80% for detecting at least a standardized mean difference of 0.1 in 25(OH) Vitamin D levels between mothers of term and preterm led to 62 participants in each group; however, we considered two controls for each case (62 mothers and their neonates with preterm and 124 controls). From September 2012 to April 2014, both cases and controls were selected randomly from women who attended to outpatients obstetric and gynecology clinics of Shahid Beheshti and Al-Zahra referral hospitals affiliated to Isfahan University of Medical Sciences, Isfahan, Iran. Inclusion criteria were as: women at reproductive age, primigravid a singleton pregnancy with gestational age of 28–42 weeks and normal pregnancy; women with gestational age of 28 weeks to <37 weeks are considered as preterm group and those with more than 37 weeks are considered as term group. Exclusion criteria include women who did not cooperate or for reasons were not able to provide cord blood or maternal blood, or women with the history of cervical insufficiency, polyhydramnios, twinning, preeclampsia, diabetes, collagen vascular disease, chronic diseases of heart, renal and pulmonary diseases, bleeding during pregnancy, embryonic abnormalities, placental and umbilical abnormalities, psychological problems, oral or genital infections, uterine anomalies, etc.

After the obtaining written informed consent from women for participating in study, a detailed history of women admitted to the labor for delivery was recorded at first, then, after ideal selection and removing the cases who did not meet inclusion criteria and had exclusion criteria, a questionnaire which included detailed information such as personal and clinical characteristics of mother and fetus were filled in. Then, 10 cc blood from mothers and 10 cc of neonate's umbilical cord was taken at birth and was immediately sent to laboratory for centrifuge, and then the serum was separated and kept in −20°C. Based on the chemiluminescence method, frozen serums were used for measuring Vitamin D levels check-in a reference laboratory (according to laboratory criteria). Those whose 25(OH) Vitamin D levels were more than 30 ng/ml was considered as sufficiency, between 10 and 30 ng/ml as insufficiency and <10 ng/ml as a deficiency.

### Statistical analysis
Categorical and continuous data were represented as frequency (percentage) and mean ± standard deviation, respectively. The normality of continuous data was evaluated using Kolmogorov–Smirnov and Q-Q plot. Nonnormal data were subjected to logarithmic transformation. Independent samples *t*-test was used for comparing the continuous data between two groups, and Chi-square or Fisher's exact tests were used for comparing categorical data between groups. Paired samples *t*-test was used for comparing Apgar score between 1st and 5 min in each study group. Kappa concordance coefficient was used for evaluating the concordance between 25(OH) Vitamin D levels status of mothers with their neonates. All statistical analyses were performed using SPSS 23 (IBM SPSS Inc., Chicago, IL, USA); $P < 0.05$ was considered as statistically significant.

## RESULTS

Table 1 presents the basic characteristics of study participants in term and preterm groups. There was no statistically significant difference between the two groups in terms of the maternal age, body mass index and type of delivery, neonates' gender ($P > 0.05$). Although the mean levels of 25(OH) Vitamin D in mothers and their neonates in preterm group were lower than term group; however, the differences were not statistically significant. As it was expected, the mean weight of neonates and their mothers in preterm group was significantly lower ($P < 0.05$).

The correlation between maternal 25(OH) Vitamin D levels and neonates was evaluated using Pearson correlation coefficient; the results have been presented in Figure 1. As can be seen, there is a significant positive correlation in both the study groups (term group: $r = 0.874$, $P < 0.001$ and preterm group: $r = 0.733$, $P < 0.001$).

Table 2 presents the concordance between 25(OH) Vitamin D levels of mothers and their neonates in both term and preterm groups. As can be seen, there is significant concordance in both groups, in which 25(OH) Vitamin D insufficiency/deficiency levels more prevalent in those neonates whose mothers had 25(OH) Vitamin D's insufficiency/deficiency ($P < 0.001$).

The neonates' Apgar test at 1 and 5 min after birth in the term and preterm groups have been evaluated and the results showed that in the preterm group it was significantly increased from $8.95 \pm 0.29$ to $9.95 \pm 0.25$ ($P < 0.001$) and the similar results were observed in term neonates; $8.4 \pm 1$ and $9.38 \pm 1.07$ ($P < 0.001$). Of total term neonates, 96.9% and 91.9% preterm showed increased Apgar score in 5 min compared to $1^{st}$ min that it was significantly different between two groups ($P < 0.05$).
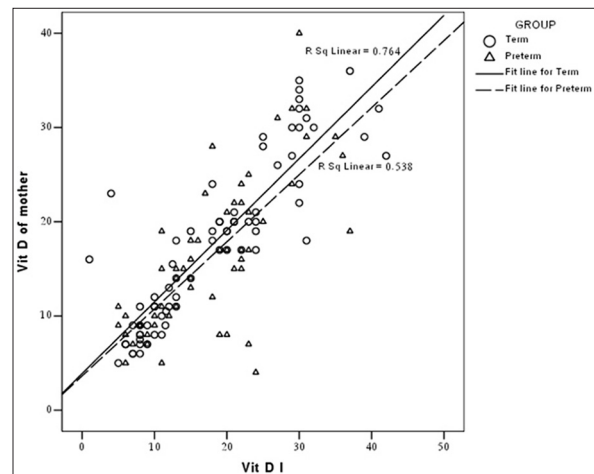
## DISCUSSION

We aimed to evaluate the association of 25(OH) Vitamin D levels of mothers and their neonates both in term and preterm delivery groups and to compare 25(OH) Vitamin D levels in mothers with term delivery versus spontaneous preterm delivery. The correlation between maternal and neonatal 25(OH) Vitamin D levels in the term and preterm group was statistically significant (term group: $r = 0.874$, $P < 0.001$ and preterm group: $r = 0.733$, $P < 0.001$). In addition, we hypothesized that preterm neonates would have lower 25(OH) Vitamin D levels than full-term ones. Our study although showed higher levels of 25(OH) Vitamin D in term neonates than preterm, but the difference was not statistically significant. Previous studies showed that lower maternal Vitamin D levels are a risk factor for preterm labor.[6] In a study among Japanese high-risk women for preterm labor, they showed significantly lower serum 25(OH) D levels ($11.2 \pm 3.2$ ng/mL vs. $15.6 \pm 5.1$ ng/mL, determined after the $30^{th}$ week of their pregnancy) in comparison with the control group).[13] Hollis *et al.*[14] reported that pregnant women supplemented with Vitamin D (400, 2000, or 4000 IU/day) at 12–16 weeks experienced lower preterm

### Table 1: Baseline characteristics of two study groups

| | Term (n=124) | Preterm (n=62) | P |
|---|---|---|---|
| Age of mother (years) | 27.12±5.79 | 27.60±5.39 | 0.630* |
| Weight of mother (kg) | 74.44±10.04 | 70.72±11.08 | 0.047* |
| Weight of neonate (kg) | 3.16±0.42 | 2.27±0.53 | <0.001* |
| Sex of neonate, n (%) | | | |
| Female | 74 (59.7) | 34 (54.8) | 0.483** |
| Male | 50 (40.3) | 28 (45.2) | |
| BMI | 28.69±3.96 | 27.84±4.53 | 0.256* |
| Delivery method, n (%) | | | |
| CS | 82 (66.1) | 28 (45.2) | 0.014** |
| ND | 42 (33.9) | 34 (54.8) | |
| Vitamin D level of mother | 17.77±8.59 | 16.26±8.11 | 0.313* |
| Vitamin D level of neonate | 18.25±9.87 | 17.58±8.36 | 0.681* |
| Maternal Vitamin D level, n (%) | | | |
| Deficiency | 32 (25.8) | 14 (22.6) | 0.545** |
| Insufficiency | 70 (56.5) | 42 (67.7) | |
| Sufficiency | 22 (17.7) | 6 (9.7) | |
| Neonatal vitamin D level, n (%) | | | |
| Deficiency | 32 (25.8) | 17 (30.6) | 0.421** |
| Insufficiency | 72 (58.6) | 39 (62.9) | |
| Sufficiency | 20 (15.6) | 4 (6.5) | |

*Resulted from independent samples *t*-test; **Resulted from Chi-square test. BMI=Body mass index; CS=Cesarean section; ND= Natural delivery



**Figure 1:** Scatter plot of maternal 25-hydroxyvitamin D levels based versus the neonatal Vitamin D in each group

### Table 2: Comparing maternal and neonatal 25-hydroxyvitamin D levels in each study group

| | Term (n=124) Neonatal 25(OH) Vitamin D levels | | | |
|---|---|---|---|---|
| **Maternal 25(OH) Vitamin D levels** | **Deficiency, n (%)** | **Insufficiency, n (%)** | **Sufficiency, n (%)** | **P*** |
| Deficiency | 25/32 (78.1) | 7/32 (21.9) | 0/32 (0) | <0.001 |
| Insufficiency | 5/70 (7.1) | 60/70 (85.8) | 5/70 (7.1) | |
| Sufficiency | 0/22 (0) | 8/22 (36.4) | 14/22 (63.6) | |
| | Preterm (n=62) Neonatal 25(OH) Vitamin D levels | | | |
| **Neonatal 25(OH) Vitamin D levels** | **Deficiency, n (%)** | **Insufficiency, n (%)** | **Sufficiency, n (%)** | **P*** |
| Deficiency | 11/14 (84.6) | 2/14 (15.4) | 0/14 (0) | <0.001 |
| Insufficiency | 8/42 (19.0) | 32/42 (76.2) | 2/42 (4.8) | |
| Sufficiency | 0/6 (0) | 4/6 (66.7) | 2/6 (33.3) | |

*Resulted from κ statistics. 25(OH) Vitamin D=25-hydroxyvitamin D

labor/birth rates. Interestingly, this effect was dose dependent.[14]

Low maternal serum 25(OH) Vitamin D levels have also been associated with a low birth weight and a small for gestational age (SGA). Leffelaar *et al.* based on data from the multi-ethnic Amsterdam Born Children and their Development cohort, on 3730 women of various ethnicities concluded that the women with first-trimester 25(OH) Vitamin D levels of 12 ng/mL or less were at higher risk (odds ratio = 2.4) of delivering SGA infants with lower birth weights than women with first-trimester 25(OH)D levels of 20 ng/mL or more.[15] Bodnar *et al.*[16] reported U-shape relationship between maternal serum 25(OH) Vitamin D levels before the 22nd week of pregnancy and the risk of SGA among Caucasian women. Leffelaar *et al.*, in the Netherlands and Bowyer *et al.*, in Australia showed that the term delivery was more common among women with higher Vitamin D levels compared to those with lower Vitamin D levels.[15,17] Burris *et al.* in contrast with our findings described compared with more mature infants, those born before 32 weeks' gestation had higher odds of umbilical cord plasma 25(OH) D levels below 20 ng/ml and described the distribution of umbilical cord plasma 25(OH) D levels at birth across the gestational age spectrum and also highlights the high risk of low levels among very preterm infants.[18]

Although Yang *et al.* reported that maternal Vitamin D level did not cause of preterm delivery,[19] some other studies recently demonstrated most of the preterm neonates had vitamin insufficiency.[20] Low 25(OH) Vitamin D levels in pregnancy have been associated with poor neonatal, maternal outcomes and Vitamin D supplementation decrease this risk.[21] Preterm infants have an even shorter duration to accumulate Vitamin D stores as well as less fat tissue for fat-soluble vitamin storage *in utero*.[4] These infants will also likely have issues related with prematurity and will be on parenteral nutrition, which will not reach target goal 400–800 IU/day until they are 2.5 kg.[22-25]

Some limitations of our study were small sample size and lack of data about the Vitamin D supplementation during pregnancy period by women included in the current study for considering it as one of the important confounders.

## CONCLUSION

Our study did not show a significant difference between two groups in terms of Vitamin D status both in mothers and neonate while the significant association was found between Vitamin D levels of mothers and neonates in both groups. These findings confirmed the previous studies' findings that Vitamin D levels in neonates could be predicted from their mothers. As a result, successful Vitamin D and calcium supplementation for improving 25(OH) Vitamin D levels in the maternal and neonatal populations for protecting the harmful effects of Vitamin D insufficiency/deficiency are recommended.

**Conflicts of interest**
There are no conflicts of interest.

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