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## OBSTETRICS

# Prevalence of Maternal Hypovitaminosis D and Obstetric Outcomes at Chonprathan Hospital, Nonthaburi, Thailand

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### ABSTRACT

**Objectives:** The primary aim of this study was to determine the prevalence of maternal hypovitaminosis D. The secondary aim was to determine the obstetric outcomes between a group of pregnant women with hypovitaminosis D and the normal control group at Chonprathan Hospital, Nonthaburi province of Thailand.

**Materials and Methods:** This study was a cross-sectional study. A total of 77 subjects were consecutively enrolled in the study. The inclusion criteria were pregnant women who had received antenatal care and delivered at Chonprathan Hospital, Nonthaburi, Thailand. The exclusion criteria included women who had a liver disease, kidney disease, gastrointestinal absorption disease, pulmonary tuberculosis, hyperthyroid disease, and pregnant women who used drugs that have an effect on vitamin D. Vitamin D deficiency was defined as 25-hydroxyvitamin D (25-OHD) < 20 ng/mL, insufficiency as 25-OHD 20–29.9 ng/mL, and sufficiency as 25-OHD ≥ 30 ng/mL. Hypovitaminosis D refer to vitamin D deficiency plus vitamin D insufficiency. A data interview was performed and the results recorded in a case record form by the research team. Venous blood samples were collected for 25-OHD, parathyroid hormone (PTH), calcium, phosphate, alkaline phosphatase (ALP), albumin, and magnesium on the day of labor.

**Results:** The mean level of 25-OHD was 25.2% ± 7.9 ng/mL. The prevalence of vitamin D deficiency was 22.1%, vitamin D insufficiency was 44.1%, and vitamin D sufficiency was 33.8%. There was an association between vitamin D level and serum albumin but no association with the other blood parameters statuses (correct calcium,PTH, phosphate, ALP, magnesium,hematocrit), age, pre-pregnancy body mass index, or obstetric complications.

**Conclusion:** The prevalence of hypovitaminosis D was 66.2%, while vitamin D deficiency was 22.1%. There was no association between the vitamin D level and obstetric outcomes.

**Keywords:** vitamin D deficiency in pregnancy, vitamin D insufficiency in pregnancy, obstetric outcomes.

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# *ความชุกของภาวะการขาดวิตามินดีในสตรีตั้งครรภ์ และผลกระทบต่อการตั้งครรภ์ ณ โรงพยาบาลชลประทาน จังหวัดนนทบุรี ประเทศไทย*

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***บทคัดย่อ***

***วัตถุประสงค์:*** *วัตถุประสงค์หลักเพื่อศึกษาถึง ความชุกของภาวะการขาดวิตามินดีในสตรีตั้งครรภ์ วัตถุประสงค์รองคือ เพื่อศึกษาผลกระทบต่อการตั้งครรภ์ในสตรีกลุ่มที่มีภาวะขาดวิตามินดีเปรียบเทียบกับกลุ่มปกติ ณ โรงพยาบาลชลประทาน จังหวัดนนทบุรี ประเทศไทย*

***วัสดุและวิธีการ:*** *การวิจัยนี้เป็นการศึกษาแบบตัดขวาง จำนวนกลุ่มตัวอย่างทั้งหมด 77 คน ถูกเลือกโดยการเรียงต่อกันตามลำดับ โดยมีเกณฑ์การคัดเข้าร่วมงานวิจัย คือ สตรีตั้งครรภ์ที่ได้รับการฝากครรภ์และคลอด ณ โรงพยาบาลชลประทาน มีเกณฑ์การคัดออก คือ สตรีตั้งครรภ์ที่มีโรคตับ, ไต, ทางเดินอาหาร, วัณโรคปอด, ไทรอยด์ และสตรีตั้งครรภ์ที่รับประทานยาที่มีผลต่อระดับวิตามินดี ภาวะพร่องวิตามินดี คือ ระดับวิตามินดีในเลือดน้อยกว่า 20 นาโนกรัมต่อมิลลิลิตร ภาวะวิตามินดีไม่เพียงพอ คือ วิตามินดีในเลือดอยู่ระหว่าง 20-29.9 นาโนกรัมต่อมิลลิลิตร และภาวะวิตามินดีปกติ คือ วิตามินดีในกระแสเลือดมากกว่าหรือเท่ากับ 30 นาโนกรัมต่อมิลลิลิตร นิยามภาวะขาดวิตามินดี คือ ภาวะพร่องวิตามินดีและ ภาวะวิตามินดีไม่เพียงพอ กลุ่มตัวอย่างจะถูกสมภาษณ์ข้อมูลเพื่อบันทึกในใบบันทึกข้อมูล และเจาะเลือดเพื่อส่งตรวจระดับวิตามินดี พาราไทรอยด์ฮอร์โมน แคลเซียม ฟอสเฟส อัลคาไลนฟอสฟาเตส อัลบูมิน และแมกนีเซียม ในวันที่มาทำการคลอด*

***ผลการศึกษา:*** *พบว่าค่าเฉลี่ยของระดับวิตามินดีเท่ากับร้อยละ 25.2 ± 7.9 นาโนกรัมต่อมิลลิลิตร ความชุกของภาวะพร่องวิตามินดีเท่ากับ ร้อยละ 22.1 ภาวะวิตามินดีไม่เพียงพอ ร้อยละ 44.1 และภาวะวิตามินดีเพียงพอ ร้อยละ 33.8 พบความสัมพันธ์ระหว่างระดับวิตามินดีกับอัลบูมิน แต่ไม่พบความสัมพันธ์ระหว่างวิตามินดี กับ ค่าแคลเซียม พาราไทรอยด์ฮอร์โมน ฟอสเฟส อัลคาไลนฟอสฟาเตส แมกนีเซียม และฮีมาโตคริท รวมทั้งไม่พบความสัมพันธ์ระหว่างระดับวิตามินดีกับอายุ น้ำหนักก่อนตั้งครรภ์ และภาวะแทรกซ้อนระหว่างตั้งครรภ์ในสตรีกลุ่มตัวอย่าง*

***สรุป:*** *พบความชุกของภาวะขาดวิตามินดี ร้อยละ 66.2 และภาวะพร่องวิตามินดี ร้อยละ 22.1 จากการศึกษาไม่พบความสัมพันธ์ระหว่างระดับวิตามินดีในกระแสเลือดและผลลัพธ์ทางสูติศาสตร์*

***คำสำคัญ:*** *ภาวะพร่องวิตามินดีในสตรีตั้งครรภ์, ภาวะวิตามินดีไม่เพียงพอในสตรีตั้งครรภ์, ผลลัพธ์ทางสูติศาสตร์*

## Introduction

There are many research studies in the literature showing that vitamin D is a beneficial nutrient for pregnant women and their babies. Studies have found the vitamin D receptor in various types of tissues in the human body, which suggest that vitamin D is not only useful for the bone-building system, but it also has benefits for the human body in other systems[1].

Vitamin D can be synthesized through human skin when skin is exposed to ultraviolet B-light or it can be absorbed from the intestines through the diet. Currently, the 25-hydroxyvitamin D (25-OHD) level measurement method is used to assess the vitamin D level in the human body[2].

Vitamin D in pregnant women plays an important role in both the mothers and babies. Vitamin D deficiency is often common in Northern Europe[1,3]. A recent study found that vitamin D deficiency is often common in pregnant women with certain risk factors, such as vegetarian groups, no or low sun-exposure groups, and especially women in dark-skin groups[4].

Some studies have found that vitamin D deficiency in pregnant women can have an effect on their pregnancy, such as preeclampsia[5], preterm labor[6], or gestational diabetes mellitus[7], and also have an effect on their infant, such as neonatal seizure due to hypocalcemia[8].

In Southeast Asian countries, especially Thailand, studies on vitamin D deficiency in pregnant women and its effects are limited. However, such studies are important as studying the prevalence of vitamin D deficiency will be guided to understanding the size of the problem and will inform guidelines for planning, prevention, and treatment in the future to overcome the problem.

The primary objective of this study was to determine the prevalence of maternal hypovitaminosis D. The secondary objective was to determine the obstetric outcomes between a group of pregnant women with hypovitaminosis D and the normal control group at Chonprathan Hospital, Nonthaburi province of Thailand.

## Materials and Methods

This study was a cross-sectional study regarding the prevalence of vitamin D deficiency in pregnant women who had delivered at Chonprathan Hospital since 2016-2017. The study was approved by the Institutional Review Board of Chonprathan Hospital, Srinakharin Wirot University, Thailand. A total of 77 subjects were consecutively enrolled in the study. The inclusion criteria were pregnant women who had received antenatal care and delivered at Chonprathan Hospital. Informed consent was obtained from all subjects. The study was performed during the period October 2016-March 2017. The exclusion criteria included women who had a liver disease, kidney disease, gastrointestinal absorption disease, pulmonary tuberculosis, hyperthyroid disease, and pregnant women who used drugs that had an effect on vitamin D, such as anticonvulsant and steroid drugs. History taking and a physical examination were used to identify the exclusion criteria among participants. The volunteer group received a detailed description of the project. A data interview was performed and the results recorded in a case record form by the research team. The interview consisted of two parts: part 1- interview to record age, weight before pregnancy, height, underlying disease, regular medications, prenatal vitamins and minerals taken, pregnancy and previous pregnancy outcomes, duration of pregnancy, delivery methods and delivery complications of previous pregnancy, and pregnancy records for infants whose weight was above 4,000 grams or less than 2,500 grams; and part 2 – interview to record labor issues, including delivery methods, color of amniotic fluid, blood loss during delivery, and maternal and neonatal complications during pregnancy and labor (e.g., gestational hypertension (HT), preeclampsia, gestational diabetes mellitus (GDM), postpartum hemorrhage (PPH), preterm labor). Venous blood collection was performed for 25-OHD, parathyroid hormone (PTH), calcium, phosphate, alkaline phosphatase (ALP), albumin, and magnesium on the

day of labor. The time of interview was the same as the time of blood sampling. Gestational ages of participants were $36^{+1}$ to 41 weeks.

The researchers asked the interviewees about taking iron supplementation (e.g., natural, ferrous fumarate, and obimin AZ®) and confirmed with the out patient department card whether they took the supplementation reported in the interview. This was important as iron supplementation typically contains vitamin D; for instance, natural, ferrous fumarate, and obimin AZ® contain 400 IU vitamin D, so this can affect the vitamin D status of pregnant women.

Vitamin D deficiency was defined as 25-OHD < 20 ng/mL, insufficiency as 25-OHD 20-29.9 ng/mL, and sufficiency as 25-OHD ≥ 30 ng/m[9]. Hypovitaminosis D was defined as vitamin D deficiency plus vitamin D insufficiency.

Obstetric outcomes of this study included gestational HT, preeclampsia, GDM, PPH, fetal growth disorder, preterm birth, premature rupture of membranes, fetal distress, breech presentation, placenta previa, consumptive coagulopathy.

The sample size was calculated by using the formula:

$$n = \frac{Z^2_{\alpha/2} pq}{d^2} \quad \text{where} \quad Z_{\alpha/2} = 1.96$$

p = Prevalence of maternal hypovitaminosis D among pregnant women in the Thai population (75%), q = 1-p, d = The absolute error of the sample size (equal to 15%)

$$n = \frac{1.96^2 0.75 \times (1 - 0.75)}{(0.15 \times 0.75)^2} = 57$$

According to Pratumvinit, et al[10], the prevalence of maternal hypovitaminosis D among pregnant women in Bangkok, Thailand is 75.5%. The data collected for any missing data were 20%. Therefore, the sample size of this study was 69 people.

The plasma levels of calcium, phosphate, ALP, albumin, and magnesium were measured using an automated analyzer (Cobas C501, Roche Diagnosis, Germany). Intact PTH levels were measured using a chemiluminescent microparticle immunoassay (Abott Diagnostics, Wiesbaden, Germany). 25-OHD levels were analyzed using a chemiluminescent microparticle immunoassay (Abbott Diagnostics, Longford, Ireland). The laboratory investigation used 3 ml of blood for analysis in the laboratory at Panyananthphikkhu Chonprathan Medical Center. The inter-and intra-assay coefficient variant of 25-OHD test were 2.4% and 1.1%, respectively.

Statistic analysis was performed using SPSS version 17. Descriptive statistic (mean, percent, frequency and standard deviation) were used. Independent t test was used to compare mean of investigated factors between hypovitaminosis D group and control group. Fisher exact test were used to compare the percent of obstetric complications between hypovitaminosis D group and control group. A p value < 0.05 was considered statistically significant.

## Results

In total, 77 pregnant women were included in the study. The mean age was 27.3 ± 6.1 years. Primiparity and multiparity were 42.9% and 57.1%, respectively. The mean weight and height were 53.6 ± 10.9 kg and 157.7 ± 6.2 cm, respectively. The pre-pregnancy body mass index (BMI) values in the range of underweight, normal weight, overweight, and obesity equivalents were 17.3%, 66.7%, 13.3%, and 2.7%, respectively. The mean gestational age was 38.6 ± 1.1 weeks. The women with blood group A, B, AB and O were 26%, 36.4%, 3.9%, and 33.8%, respectively. There was no Rhesus negative pregnant woman in this study.

Table 1 demonstrates blood chemistry status in this study. Mean level of 25-OHD, intact PTH, correct calcium, albumin, magnesium, phosphate, ALP were 25.2 ± 7.9 ng/mL, 40.8 ± 22.4 pg/mL, 8.9 ± 0.4 mg/dL, 3.58 ± 0.27 g/dL, 1.93 ± 0.18 mg/dL, 4.7 ± 2.8 mg/dL and 165.2 ± 51.5 unit/L, respectively.

The prevalence of vitamin D deficiency was 22.1%, vitamin D insufficiency was 44.1%, and vitamin D sufficiency was 33.8% (Table 2).

**Table 1.** Blood chemistry status of pregnant women in Chonprathan Hospital.

| Blood chemistry | Normal range in pregnancy (3rd trimester) | Mean | Standard deviation |
|---|---|---|---|
| 25-OHD (ng/mL) | 10 - 18 | 25.2 | 7.9 |
| Intact PTH (pg/mL) | 9 - 26 | 40.8 | 22.4 |
| Correct calcium (mg/dL) | 8.8 - 10.3 | 8.9 | 0.4 |
| Albumin (g/dL) | 2.3 - 4.2 | 3.58 | 0.27 |
| Magnesium (mg/dL) | 1.1 - 2.2 | 1.93 | 0.18 |
| Phosphate (mg/dL) | 2.8 - 4.6 | 4.7 | 2.8 |
| ALP (unit/L) | 38 - 229 | 165.2 | 51.5 |

PTH: parathyroid hormone, ALP: alkaline phosphatase.

**Table 2.** Vitamin D status in pregnant women.

| Vitamin D status in pregnancy | Number (total 77) | Prevalence (%) |
|---|---|---|
| Vitamin D sufficiency (25-OHD ≥ 30 ng/L) | 26 | 33.8 |
| Vitamin D insufficiency (25-OHD 20-29.9 ng/L) | 34 | 44.1 |
| Vitamin D deficiency (25-OHD < 20 ng/L) | 17 | 22.1 |

OHD: hydroxyvitamin D

There was an association between the vitamin D level and albumin, but no association with the other blood parameters statuses (correct calcium,PTH, phosphate, ALP, albumin, magnesium, hematocrit), age, pre-pregnancy BMI, or obstetric complications (gestational HT, preeclampsia, GDM, PPH, fetal growth disorder, preterm birth, premature rupture of membranes, fetal distress, breech presentation, placenta previa, consumptive coagulopathy) (Table 3, 4).

**Table 3.** Compare mean of investigated factors associated with 25-hydroxyvitamin D.

| Factors | n | Hypovitaminosis D (25-OHD < 30 ng/mL) | n | Vitamin D sufficiency (25-OHD ≥ 30 ng/mL) | p value |
|---|---|---|---|---|---|
| Age (years) | 51 | 27.41 ± 6.35 | 26 | 27.04 ± 5.60 | 0.801 |
| Gestational age (weeks) | 51 | 38.77 ± 1.18 | 26 | 38.75 ± 0.09 | 0.953 |
| Pre-pregnancy BMI (kg/m2) | 51 | 21.92 ± 4.05 | 26 | 21.02 ± 3.77 | 0.351 |
| Pregnant BMI (kg/m2) | 51 | 27.62 ± 4.17 | 26 | 26.23 ± 3.92 | 0.163 |
| PTH (mg/dL) | 51 | 43.86 ± 23.08 | 26 | 34.89 ± 20.24 | 0.097 |
| Correct calcium (mg/dL) | 51 | 9.29 ± 0.43 | 26 | 9.25 ± 0.44 | 0.714 |
| Phosphate (mg/dL) | 51 | 4.48 ± 2.62 | 26 | 5.14 ± 3.08 | 0.332 |
| ALP (unit/L) | 51 | 169.2 ± 56.04 | 26 | 157.38 ± 41.15 | 0.345 |
| Albumin (g/dL) | 51 | 3.52 ± 0.26 | 26 | 3.69 ± 0.25 | 0.008 |
| Magnesium (mEq/L) | 51 | 1.91 ± 0.18 | 26 | 1.95 ± 0.19 | 0.391 |
| Hematocrit (%) | 51 | 35.23 ± 3.32 | 26 | 35.17 ± 2.28 | 0.935 |
| Platelets (/mm3 ) | 51 | 284,449.02 ± 65,567.39 | 26 | 257,076.92 ± 56,586.87 | 0.074 |
| Blood loss (mL) | 51 | 332.35 ± 210.43 | 26 | 338.46 ± 196.63 | 0.902 |

Data presented as mean ± standard deviation or n (%), OHD: hydroxyvitamin D, BMI: body mass index, ALP: alkaline phosphatase

**Table 4.** Comparison of the number (%) of obstetric complications between hypovitaminosis D group and a non-hypovitaminosis D group.

| Obstetrics complications | n | Hypovitaminosis D (25-OHD < 30 ng/mL) n (%) | n | Vitamin D sufficiency (25-OHD > 30 ng/mL) n (%) | p value |
|---|---|---|---|---|---|
| Gestational HT | 51 | 0 (0%) | 26 | 0 (0%) | NA |
| Preeclampsia | 51 | 0 (0%) | 26 | 0 (0%) | NA |
| GDM A1 | 51 | 0 (0%) | 26 | 1 (3.8%) | 0.338 |
| GDM A2 | 51 | 0 (0%) | 26 | 0 (0%) | NA |
| PPH | 51 | 2 (3.9%) | 26 | 0 (0%) | 0.547 |
| IUGR | 51 | 0 (0%) | 26 | 0 (0%) | NA |
| Preterm birth | 51 | 1 (2.0%) | 26 | 0 (0%) | 1 |
| Premature rupture of membranes | 51 | 3 (5.9%) | 26 | 0 (0%) | 0.547 |
| Fetal distress | 51 | 1 (2.0%) | 26 | 0 (0%) | 1 |
| Breech presentation | 51 | 5 (9.8%) | 26 | 2 (7.7%) | 1 |
| Placenta previa | 51 | 1 (2%) | 26 | 0 (0%) | 1 |
| Coagulopathy | 51 | 0 (0%) | 26 | 0 (0%) | NA |

OHD: hydroxyvitamin D, HT: gestational hypertension, GDM: gestational diabetes mellitus, PPH: postpartum hemorrhage, IUGR: intrauterine growth restriction

## Discussion

Thailand is a country in Southeast Asia, and near the equator, so it experiences relatively strong sunlight throughout the year. Despite this, World Health Organization found the incidence of vitamin D deficiency in Thailand is relatively high. The present study discovered that the prevalence of vitamin D insufficiency (25-OHD 20-29 ng/mL) and vitamin D deficiency (25-OHD < 20 ng/mL) were 44.1% and 22.1%, respectively. The prevalence of hypovitaminosis D in this study was 66.2%, which is slightly different from one study in Bangkok showed that the prevalence of hypovitaminosis D (25-OHD < 30 ng/mL) was 75.5%[10]. However, the study from Thammasart university, Pathumthani province, Thailand found the prevalence of vitamin inadequacy (25-OHD < 75 nmol/L, which approximately < 24 ng/mL) was only 27.4% in third trimester pregnancy[11].

Our study found that serum albumin was the factor that associated with hypovitaminosis D. However mean serum albumin level in hypovitaminosis D group was slightly lower than vitamin D sufficiency. Although, there was no association between hypovitaminosis D and intact PTH but if we analyzed only vitamin D deficiency group (25OHD < 20 ng/mL), we found the association between vitamin D deficiency group and intact PTH. The vitamin D deficient group had intact PTH level concentrations higher than in the vitamin D sufficient group, which was in accordance with the findings in other studies[10]. However, the level of intact PTH is regulated by serum ionized calcium not by 25-OHD[12]. This phenomenon may have been because the intact PTH response to a low level of 25-OHD was reduced by the higher levels of calcium in women without secondary hyperparathyroidism[13]. The present study found no relationship between serum correct calcium level and vitamin D status.

Our study found no relationship between BMI before pregnancy and vitamin D status, in contrast with one study that showed that BMI had a significant effect

on vitamin D status. They explained that a person with a high BMI usually has a high content of body fat, which acts as a reservoir for lipid-soluble vitamin D. At the same time, lipid-soluble vitamin D release from fat is extremely slow. Excess body fat results in its increased sequestration and low availability and, as a consequence, low serum 25-OHD level[14]. The reason that there was no relationship found with BMI before pregnancy in our study might due to the limited sample size, as the obesity group represented only 2.7% of our sample set.

In terms of the maternal outcome, in our study, we were unable to find an association between vitamin D deficiency and meconium status, fetal distress, mode of delivery, preterm birth, or premature rupture of the membranes. One systematic review and meta-analysis result was opposite that found in our study concerning preterm birth. They found that vitamin D deficiency was associated with preterm birth, with serum 25-OHD levels < 75 nmol/l associated with an 83% (95%CI 1.23, 2.74) and 13% (95%CI 0.94, 1.36) increased risk of preterm birth measured at < 32 - 34 weeks and < 35 - 37 weeks, respectively[15]. However, from study by Bhupornvivat and Phupong found that the serum 25-OHD concentrations and the prevalence of vitamin D deficiency and insufficiency were not different between the preterm labor and the term labor groups[16]. Therefore, study about vitamin D deficiency and preterm birth is needed in this area in the future.

The results from many studies have shown no association between a premature rupture of the membranes and vitamin D deficiency, which is consistent with our study[17].

A study concluded that vitamin D levels were significant lower in a mother delivering by cesarean section due to suspected fetal distress and birth asphyxia[18], which is contrast to the results from our study. However, our study had a limited number of fetal distress cases, indeed only one case from our 77-sample set.

Although we concluded that vitamin D deficiency has a high prevalence, there was no relation between vitamin D deficiency and obstetric complications. Due to the limited evidence currently available to directly assess the benefits and harms of the use of vitamin D supplementation alone in pregnancy for improving maternal and infant health outcomes, the use of this intervention during pregnancy as part of routine antenatal care is not recommended. This study related to the suggestion from WHO 2016 that vitamin D supplementation is not recommended for pregnant women, and to improve maternal and perinatal outcome, pregnant women should instead be encouraged to receive adequate nutrition, which is best achieved through the composition of a healthy and balanced diet. For pregnant women with documented vitamin D deficiency, vitamin D supplements may be given at the current recommended nutrient intake of 200 IU (5 micrograms) per day[19,20].

The strength of this study was the first study about the prevalence of hypovitaminosis D in Nonthaburi province, urban area in Thailand. This study confirmed that there had high prevalence of hypovitaminosis D in this area. However, the limitation of this study was a few of participants had the level of 25-OHD less than 20 ng/mL which may deter us from finding the correlation between vitamin D deficiency and adverse obstetric outcome.

## Conclusion

There is a high prevalence of vitamin D deficiency in pregnant women at Chonprathan Hospital, Nonthaburi, Thailand. However, there was no relation between hypovitaminosis D and adverse obstetric outcomes. Therefore, it should not recommend prescribing vitamin D supplementation for pregnant women attending Chonprathan Hospital for antenatal care.

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## Potential conflicts of interest

The authors declare no conflict of interest.

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