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# Late Onset Hypocalcemia and Hypovitaminosis D in Neonates from Maternal Hypovitaminosis D

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## ABSTRACT

Hypocalcemia, characterized by low blood calcium levels, poses serious risks, particularly for neonates and pregnant women. Maternal calcium and vitamin D deficiencies during pregnancy can hinder fetal skeletal development and increase neonatal hypocalcemia risk, especially in premature infants or those born to diabetic mothers. Studies highlight a high prevalence of neonatal hypocalcemia linked to inadequate maternal supplementation, underscoring the importance of calcium and vitamin D during pregnancy. Understanding maternal and neonatal calcium-vitamin D balance is essential for developing preventive strategies to ensure healthy neonatal growth. This case report explores recurrent hypocalcemia and hypovitaminosis D in neonates born to vitamin D-deficient mothers. A 1 month-old boy with hypovitaminosis D and a history of recurrent hypocalcemia since one week of age. The patient had repeated seizures at the age of 6 days without fever and hypoglycemia, the overall physical examination was within normal, the results of the lumbar puncture were within normal limits. Laboratory examinations at that time showed low of serum calcium, urinary calcium, calcium ion and vitamin D levels, while magnesium, phosphorus and parathyroid hormone (PTH) levels were within normal limits. The patient was given vitamin D therapy, calcium lactate, and intravena calcium correction was performed. The case highlights maternal vitamin D deficiency, obesity, and hyperglycemia during pregnancy as contributing factors. Adequate prenatal care, nutritional support, and vitamin D supplementation for mothers are critical to preventing neonatal complications. Family education and multidisciplinary care are essential for managing hypocalcemia and ensuring long-term health outcomes.

***Keywords:*** *Seizures; hypocalcemia; hypovitaminosis D; neonates; maternal*

## INTRODUCTION

Hypocalcemia, characterized by low calcium levels in the blood, can seriously affect health. Though less common than hypercalcemia, it can be life-threatening if not properly addressed. The causes of hypocalcemia are diverse, often involving interactions between parathyroid hormone, phosphorus metabolism, vitamin D, and bone metabolism.[1] Calcium, essential for forming bones and teeth, is mainly stored in bones, with a small portion in the extracellular fluid.[2,3]

In pregnancy, hypocalcemia is linked to inadequate nutrition, hyperemesis gravidarum, and pre-existing conditions. During pregnancy, fetal calcium is transferred through a calcium pump regulated by parathyroid hormone-related

peptide (PTHrP), especially in the third trimester when fetal growth and bone development are rapid. This process leads to fetal hypercalcemia, ensuring adequate skeletal mineralization and supporting fetal development.[4]

Neonatal hypocalcemia can affect premature infants, those born to diabetic mothers, and those with perinatal asphyxia. In diabetic infants, rapid growth increases calcium demand, while in premature infants, interrupted calcium transport leads to hypocalcemia. In asphyxiated infants, renal insufficiency, metabolic acidosis, and reduced parathyroid hormone secretion contribute to the condition.[2,3,5]. A study of 100 neonates revealed a 76% prevalence of hypocalcemia, with 52% progressing to late-onset hypocalcemia. A significant number of affected neonates had no vitamin D supplementation and were born to mothers who received no calcium supplementation.[6]

Maternal nutrition, particularly calcium and vitamin D intake during pregnancy, directly impacts neonatal calcium status.[7,8] This case report explores the relationship between maternal and neonatal vitamin D levels and their role in neonatal hypocalcemia.

## CASE PRESENTATION

A 23-day-old boy was referred to a regional hospital with the diagnosis of recurrent hypocalcemia and epilepsy. Since the age of 6 days, the child had experienced recurrent seizures, 5-10 times per day, lasting approximately 30 seconds, the eyes were blinking, the legs and arms were like pedaling a bicycle, the child was conscious after the seizure. There were no fever or history of fever, blood glucose was normal during seizures, and this was the first episode. There was no cough, runny nose, nor shortness of breath. There were no signs of bleeding in the skin, gums, nose, and gastrointestinal tract. There was no vomiting, nor history of the previous vomiting. The child had no history of anemia. Vitamin K injection was given at birth. There was a history of jaundice at the age of 4-9 days, the jaundice disappeared on its own without phototherapy. During treatment in the NICU, the lowest blood calcium was 5 mg/dl.

The infant was delivered via cesarean section due to macrosomia, with a birth weight of 4900 grams. The mother had a history of hyperglycemia during pregnancy, with blood glucose levels >200 mg/dL in the first trimester, treated temporarily. The mother had obesity and was 38 years old when she had pregnant. The mother was known to suffer from hypovitaminosis D with a vitamin D level of 12.7 ng/mL and calcium ion of 1.17 mmol/L. The mother was taking vitamin D supplementation at the time the child was referred to the hospital.

Physical examination showed that the patient was generally well, alert and the blood pressure, pulse rate, respiratory rate, body temperature were all within normal limits. The nutritional status was good with a bodyweight of 4.5 kg, body height of 52 cm. The child did not appear anemic, nor cyanosis. There was no edema, nor jaundice. The head shape was round and symmetrical, with a head circumference of 35 cm (normal per Nelhaus standards), the major fontanelle was still open and palpable flat. Hair was black and not prone to falling out. The conjunctiva was not pale, sclerae were non-icteric, pupils were isocoric (2 mm/2 mm) with normal light reflex. No lymphadenopathy, ear abnormalities, or enlarged tonsils were noted. Oral mucosa was moist. The chest appeared normal, with symmetrical movement and bronchovesicular breath sounds without rales or wheezes. The heart had a regular rhythm, no palpable apical impulse, and no murmurs. The abdomen was non-distended, soft, with no palpable liver or spleen, and normal bowel sounds. Genital examination showed bilateral testicular descent, and pubertal status was A1P1G1. The extremities were warm, with good perfusion, no edema, normal physiological reflexes, and no pathological reflexes. No abnormalities were found in the anus or genitalia.

The head and urology ultrasound were within normal. The results of the lumbar puncture were not in accordance with meningitis, on the investigation of hypocalcemia at that time, the urinary calcium was 14.3 mg/24 hours (reference value: 100-320 mg/24 hours); calcium ion was 0.17 (reference value: 1.17-1,3); PTH was 11.2 pg/ml (reference value: 10-65 pg/mL); blood calcium was 6.3 mg/dl (reference value: 8.1-10.4 mg/dl); vitamin D level was 21.4 ng /ml (reference value: 30-100 ng/mL); magnesium was 1.7 mg/dl (reference value: 1.6-2.6mg/dl); phosphorus was 7 mg/dl (reference value: 3-7.5 mg/dl ). The lab results showed hypocalcemia and hypovitaminosis D. During treatment in the NICU, the patient received repeated intravena calcium correction

The patient was given vitamin D supplementation of 2000 IU, calcium lactate 100 mg three times daily. The patient had improved after vitamin D administration and was discharged from the hospital after 14 days, and routine check-ups at the pediatric endocrinology clinic every month. Additional investigations planned included a tuberculin skin test. Monitoring included vital signs, clinical manifestations, Denver Developmental Screening, and routine vitamin D and calcium checks. Family education focused on reinforcing the importance of proper follow-up, increasing knowledge about hypocalcemia and hypovitaminosis D, and understanding the significance of sunlight exposure and supplementation. Parents were also informed about the importance of completing immunizations and supporting the child's growth and development for optimal outcomes.

At the follow-up in 1 year old, the child had well growth and development according to his age. During the observation, the child never had a seizure and there were no signs and symptoms of rickets. He had good nutritional status with a growth rate of 25 cm/year (P97) in the first year. The child had completed basic immunizations. Routine calcium examination was carried out every 2-3 months, the results were within normal limits. Hydroxyvitamin D level of 47,4 ng/ml (sufficiency). Therapy was continued with vitamin D 2000 IU once daily, calcium lactate 100 mg three times daily, The prognosis for the patient's survival, function, and recovery was considered "dubia ad bonam".

## DISCUSSION

A case was reported of a A 23-day-old boy with late-onset hypocalcemia due to vitamin D deficiency. Vitamin D deficiency can be found in all age groups. A study by Melamed et al. in India revealed that 62-82% of children had 25-hydroxyvitamin D levels below 20 ng/ml. A study on immigrant infants from Pakistan, Turkey, and Somalia in Norway found that 47% of infants had 25-hydroxyvitamin D levels below 10 ng/ml. Of 93 children from northern Jordan (average age of 5 years), 39% had 25-hydroxyvitamin D levels below 20 ng/ml.[9]

From the patient's history, generalized seizures were reported starting at 6 days of age. According to Jain, the diagnosis of late-onset hypocalcemia appears at the end of the first week, between 3-7 days post-delivery, presenting as neonatal tetany.[10] The seizures experienced by the patient indicate irritability of the central nervous system and poor muscle contractility. Low calcium levels lower the neuronal excitation threshold, causing neurons to respond repeatedly to stimuli. Neuronal excitability occurs in both sensory and motor nerves, making hypocalcemia lead to various effects on the central nervous system, such as paresthesia, tetany, seizures, and even psychiatric changes in children.[11]

A history of jaundice at 4-9 days of age was not considered a risk factor as the patient did not undergo phototherapy. Phototherapy for hyperbilirubinemia can increase the risk of hypocalcemia by reducing melatonin secretion, leading to higher calcium uptake by bones. To prevent complications like convulsions or apnea, blood calcium levels should be closely monitored during

phototherapy. If calcium levels are low, timely supplementation is essential to ensure the infant's well-being. Proper management during phototherapy can help reduce the risk of hypocalcemia and its effects.[11,12]

Physical examination should be conducted while considering facial anomalies, cleft palate, and asymmetric crying faces, which can be seen in hypocalcemia related to syndromes. DiGeorge syndrome is one such syndrome that includes hypoparathyroidism. Patients with DiGeorge syndrome present in the first week of life with signs of hypocalcemia, such as tetany or seizures due to hypoplastic or absent parathyroid glands. DiGeorge syndrome is characterized by facial features that include a small mouth, submucous cleft palate, abnormal and low-set ears, an inverted nose, and a widened distance between the inner canthi (telecanthus) with a short palpebral fissure.[13]

In laboratory results, for the investigation of recurrent hypocalcemia, urine calcium was 14.3 mg/24 hours (reference range 100-320 mg/24 hours), blood calcium was 6.3 mg/dl (reference range 8.1-10.4 mg/dl, concurrently taken during urine calcium testing), PTH was 11.2 pg/ml, and 25-OH vitamin D was 21.4 ng/ml (reference range 30-100 ng/mL). Laboratory findings indicate vitamin D insufficiency in the child based on the Endocrine Society, which defines levels from 21 to 29 ng/mL (52.5-72.5 nmol/L).[14]

Based on family history research, it was found that the mother had obesity, a history of hyperglycemia, and vitamin D deficiency. The examination showed an ionized calcium level of 1.17 mmol/L (reference range 1.17-1.29 mmol/L) and a vitamin D level of 12.7 ng/mL (reference range 30-100 ng/mL). During the first trimester of pregnancy, the mother had a blood glucose level above 200 mg/dL, and she was given diabetes medication for 3 days (the specific medication name and type are unknown). At the following ANC visit, her blood glucose levels were within normal range, and the diabetes medication was discontinued.

The patient's vitamin D deficiency is linked to the hypocalcemia they experienced. Inadequate vitamin D (<50 nmol/L) reduces calcium absorption to 10-15%, compared to 30% in sufficient levels.[15] Maternal vitamin D deficiency is a key cause of slow-onset hypocalcemia in neonates. In Iran, all affected neonates had mothers with vitamin D deficiency.[16] Late-onset hypocalcemia in neonates can result from factors like maternal vitamin D deficiency, with preventive measures including maternal sun exposure and vitamin D supplementation. Studies show that neonates born to vitamin D-deficient mothers are at higher risk, and exclusive breastfeeding without vitamin D supplements increases this risk. High phosphate intake is also linked to late-onset hypocalcemia, emphasizing the need for proper nutrition.[17,18]

The maternal nutritional status, including calcium and phosphorus intake, pre-pregnancy BMI, and socioeconomic factors, influences the 1,25(OH)2D concentration in umbilical cord blood. Despite severe maternal vitamin D deficiency, neonates often have normal serum calcium and bone values at birth, as fetal bone mineralization relies heavily on maternal vitamin D status. The "fetal programming hypothesis" suggests that environmental factors like 1,25(OH)2D can affect fetal genomic programming and long-term disease risk, emphasizing the importance of vitamin D in intrauterine development.[19]

The patient had a history of calcium correction using calcium gluconate in previous treatment. This aligns with managing acute hypocalcemia, which involves slow intravenous administration of calcium gluconate while monitoring pulse rate and QT interval. The calcium gluconate infusion should be reduced to 50% of the initial dose over the next 24 hours and then stopped. The infusion can be replaced with oral calcium therapy on the last day.[11,20,21] Serum calcium concentrations should be monitored weekly, then at intervals of 1-3

months once stabilized. In cases of recurrent hypocalcemia, oral calcium and vitamin D supplements are needed.

In this patient, clinical improvement was noted, evidenced by the absence of seizures and increased calcium levels after administration of vitamin D 1x2000 IU and oral calcium lactate 3x100 mg. According to the Endocrine Society, children aged 1-12 months should receive 2,000 IU/day of vitamin D or 50,000 IU/week for 6 weeks, followed by a maintenance dose of 400-1,000 IU/day.[13] For asymptomatic patients or those who have achieved normo-calcemia with intravenous calcium administration, oral calcium therapy can be given. In such cases, 40-80 mg/kg/day of elemental calcium can be provided in 3-4 doses.[20]

The family was commended for attending regular check-ups and following all recommendations. The doctor should enhance the mother's awareness of potential risks if she becomes pregnant and gives birth again. The Institute of Medicine recommends 600 IU/day, the Endocrine Society recommends 1,500-2,000 IU/day, and the American College of Obstetricians and Gynecologists suggests 600 IU/day for pregnant women in general and up to 1,000-2,000 IU/day for those with vitamin D deficiency. Vitamin D supplementation of <2000 IU/day is not effective in preventing vitamin D deficiency during pregnancy and in neonates.[19]

The family was advised on the importance of vitamin D to prevent bone growth disorders and hypocalcemia symptoms like seizures and tetany. They were encouraged to consume vitamin D-rich foods such as fish, egg yolks, shrimp, liver, milk, and orange juice.[13] Vitamin D exists as D3 (cholecalciferol) and D2 (ergocalciferol), with 25-hydroxy vitamin D playing a key role in metabolism. Sources of vitamin D include fish (5-25 µg/100 g), mushrooms (21.1-58.7 µg/100 g), and fortified foods like milk, yogurt, and cereals.[22]

The family was educated on the benefits of morning sun exposure for treatment, as ultraviolet rays enable the skin to synthesize pre-vitamin D3 from 7-dehydrocholesterol. This converts to vitamin D3 (cholecalciferol) depending on temperature, though melanin production from sunlight can reduce synthesis.[23] The duration of UVB exposure is critical for achieving adequate vitamin D levels, and vitamin D fortification in foods may serve as an alternative. This is especially relevant in Indonesia, a tropical country with year-round optimal sunlight exposure, making it a "sun-rich" nation.[24]

The prognosis for hypocalcemia in this case is uncertain but optimistic. Parents have been thoroughly counseled on the condition's progression, treatment plan, and expected outcomes. Managing maternal hypoparathyroidism during pregnancy requires careful use of 1,25-(OH)2 vitamin D and a multidisciplinary approach involving endocrinologists and obstetricians for optimal care.[25]

## CONCLUSION

The conclusion of this case emphasizes the importance of early detection and management of vitamin D deficiency in infants and children, as it can lead to serious complications such as hypocalcemia, seizures, and delays in motor development. Routine check-ups, monitoring growth, and educating families about the role of vitamin D in bone health and child development are crucial. Proper treatment, including vitamin D and calcium supplementation, can improve clinical outcomes and the patient's development. Close collaboration between healthcare providers and families can enhance treatment success and prevent recurrence. Active family involvement is vital for supporting treatment, recognizing potential issues early, and ensuring the best possible health outcomes for the patient.

### *Declaration by Authors*

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