Case Report / Olgu Sunumu

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Perinatal outcomes of high-dose vitamin D administration in the last trimester

Son trimesterde yüksek doz D vitamini uygulamasının perinatal sonuçları

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Abstract

In recent years, interest in the evaluation of vitamin D levels and the possible outcomes of their deficiency during pregnancy has increased. However, there is no consensus on when to start vitamin D supplementation, its duration, dosage, and the optimum level during pregnancy. The toxicity of vitamin D is as important as its deficiency. From the history of a 5-day-old male baby who was investigated for hypercalcemia, it was learned that the mother took 300,000 IU vitamin D-five ampoules/oral at 30 weeks of gestation every other day. The infant was born prematurely, postpartum bradycardia required positive pressure ventilation, and his hypercalcemia lasted approximately 4 months despite treatment. Maternal excessive and inappropriate use of vitamin D can cause preterm labor and severe hypercalcemia, which is a life-threatening complication in the neonatal period. This case is presented to draw attention to the negative effects of maternal high-dose vitamin D during pregnancy.

Keywords: Hypercalcemia, 25 (OH) vitamin D, vitamin D intoxication, neonatal outcomes

Öz

Son yıllarda D vitamininin gebelikte değerlendirilmesi ve eksikliğinin olası sonuçlarına yönelik ilgi artmıştır. Ancak gebelikteki D vitamini desteğinin ne zaman başlanacağı, süresi, dozu ve olması gereken optimum düzeyi konusunda fikir birliği bulunmamaktadır. D vitamininin eksikliği kadar toksisitesi de önemlidir. Hiperkalsemi nedeni ile danışılan beş günlük erkek bebeğin öyküsünden annenin 30. gebelik haftasında, gün aşırı, 300.000 IU D vitamini-beş ampul/oral aldığını öğrenildi. Olgu, prematüre doğmuş, doğum sonrası bradikardi nedeni pozitif basınçlı ventilasyon gereksinimi olmuş ve hiperkalsemisi tedavilere rağmen yaklaşık dört ay sürmüştü. D vitaminin maternal aşırı ve uygunsuz dozda kullanımı; erken doğum eylemine ve yenidoğan döneminde hayatı tehdit edici bir komplikasyon olan ciddi hiperkalsemiye neden olabilmektedir. Gebelikte maternal yüksek doz D vitaminin olumsuz etkilerine dikkat çekmek amacı ile bu olgu sunulmuştur.

Anahtar Kelimeler: Hiperkalsemi, 25 (OH) vitamin D, vitamin D intoksikasyonu, yenidoğan sonuçları

Introduction

Vitamin D maintains the normal plasma levels of calcium and phosphorus and is essential for growth. Maternal vitamin D deficiency during pregnancy is known to play a role in preeclampsia, gestational diabetes mellitus, postpartum depression, low birth weight, periodontal diseases, and affects the development of the skeletal system, respiratory system, and central nervous system of the fetus[1,2]. It has been reported that vitamin D deficiency is seen in 80% of women in the reproductive period in Turkey, severe vitamin D deficiency is found in 27% of pregnant women, and 64% of cord blood[3]. However, there is no consensus on when to start vitamin D supplementation during pregnancy, the duration, dosage, and optimum level of vitamin D[1]. In recent years, there has been increased interest in the assessment of vitamin D levels during pregnancy and the possible consequences of deficiency[2]. However, its toxicity is as important as vitamin D deficiency. In this article, a case of neonatal hypercalcemia due to vitamin D intoxication after maternal high dose vitamin D intake during pregnancy will be discussed.

Case Presentation

Written informed consent was obtained from the parents of the patient. A 5-day-old male baby was referred to endocrine

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clinic due to hypercalcemia. It was learned that he was born by cesarean section due to bradycardia detected in a non-stress test, from a 33-year-old mother's first pregnancy, with 7/9 Apgar score, at 34 weeks with a birth weight of 2.140 grams. Positive pressure ventilation was applied to the baby for 15 minutes due to postpartum bradycardia. He was then admitted to the neonatal intensive care unit for prematurity and bradycardia. In intensive care follow-up, cord blood gas analysis revealed the following results: pH: 7.21, HCO_3: 14.3 meq/L, base deficit: -12.5, lactate: 9.3 mg/dL (N: 0-2). Intravenous 0.9% NaCl loading at a dose of 20 mL/kg was performed. The patient was hospitalized with a preliminary diagnosis of lactic acidosis-metabolic disease because the follow-up blood gas analysis revealed acidosis and hypoglycemia. There was no tachypnea, bradycardia, and hypoglycemia in the follow-up. There was no pathology in the amplitude-integrated electroencephalography, which was examined for the possibility of convulsions due to hypoxia. Patent foramen ovale and thin ductus were found in echocardiography, no pulmonary hypertension was detected, and the metabolic test results and eye examinations were normal.

On the postnatal fifth day, serum calcium level was 10.8 (N: 8.9-10.8) mg/dL, ionized calcium: 1.44 (N: 1-1.3) mg/dL, phosphorus: 3.5 (N: 4.5-9) mg/dL, alkaline phosphatase: 132 IU/mL, parathormone <2.5 (N: 11-67) pg/mL, and albumin was 2.9 g/dL. The follow-up calcium value increased to 12 mg/dL and ionized calcium value increased to 1.57 mg/dL. When a more detailed history was taken, it was learned that the mother took five ampoules from 300,000 IU vitamin D ampules orally every other day at her 30th gestational week with the advice of her obstetrician (1,500,000 IU/total dose). The maternal serum calcium level was 9.4 mg/dL, phosphorus: 3.2 mg/dL, parathormone: 26.1 pg/mL, 25 OH vitamin D: 143.4 ng/mL, and renal ultrasonography revealed nephrocalcinosis. In our case, hydration, thiazide diuretic, steroid and alendronate treatments were given respectively for hypercalcemia. Calcium and its related laboratory test results under treatment are presented in Table 1. In the follow-up of the patient, the 25 OH vitamin D levels gradually decreased; however, hypercalcemia persisted for 3.5 months and crystalloidosis was detected in the imaging of the kidneys, and elevated platelet and troponin levels were detected during follow-up.

Discussion

Vitamin D deficiency in pregnant women is a global public health problem. It is known that maternal vitamin D deficiency during pregnancy has many negative consequences[1,2,4]. 1.25-OH vitamin D levels start to increase from the first weeks of pregnancy to maintain intrauterine calcium homeostasis. The increase in 1.25-OH vitamin D during pregnancy has been associated with increased intestinal calcium absorption. Maternal 25-OH vitamin D crosses the placenta and is the main source of vitamin D for the fetus. It has also been reported that there is an increase in vitamin D-binding protein levels during pregnancy and therefore a decrease in free vitamin D levels[4]. Although vitamin D supplementation is recommended to all pregnant women, there is no consensus on the optimum dose and duration[1].

The mother of our patient was given five ampoules of 300,000 units vitamin D during the last trimester. The vitamin D ampoules were thought to be 30,000 units by the gynecologist. When he was considering giving a total amount of 150,000 units of vitamin D, he had inadvertently administered a 10-fold dose. As a result, it was determined that the mother's vitamin D levels increased to intoxication levels with 142 ng/mL and developed nephrocalcinosis and preterm labor when our case was evaluated due to hypercalcemia. In addition, although our patient's vitamin D levels decreased, his hypercalcemia returned to normal after a long time despite treatment and his troponin levels and platelet counts were also high for an extended period. We present this case to emphasize that intrauterine vitamin D intoxication (maternal administration of vitamin D at 30 weeks of gestation, delivery at 34 weeks of gestation, intrauterine exposure of toxic vitamin D doses for 4 weeks) affect the set points of vitamin D in the fetus (e.g. 24,25 hydroxylase activity, which is responsible for vitamin D degradation and calcium receptor sensitivity). The changes in set points prolong the treatment process; caution should be taken with vitamin D supplementation during pregnancy.

Hashemipour et al.[5] divided pregnant women with vitamin D levels below 30 ng/mL at 24-26 weeks of gestation into two groups. The first group received 200 mg of calcium and 400 units/day of vitamin D and the second group was administered an additional 50,000 units of vitamin D weekly. They found that the mothers who received an additional 50,000 units/week vitamin D for 8 weeks after 24-26 weeks had more weight gain and that their infants had better growth compared with the group that did not take the additional dose[5]. In a study in which breastfeeding mothers used vitamin D for 3 months at a dose of 4.000 units/day or 60,000 units/month, no evidence of toxicity was reported in both mothers and infants receiving breast milk[6,7]. In our case, the mother used 5 ampoules of 300,000 IU vitamin D (total 1,500,000 IU) every other day in the last five weeks of gestation and gave birth to her baby with fetal distress due to preterm labor at 34 weeks of gestation. In the literature, there is a case report of a woman who took 300,000 units of vitamin D weekly (5 ampoules as prescribed in our case) in the last 40 days of pregnancy. Her baby's serum Ca levels were found to be 19.2 mg/dL at the age of nine days, and the mother and the baby's vitamin D levels were 430 and 480 ng/dL, respectively. It was emphasized that hypercalcemia improved with hydration, furosemide, and prednisolone treatments[8]. This is another case of neonatal vitamin D intoxication due to intrauterine vitamin D exposure to toxic levels in the literature. Term birth at normal weight was achieved because the exposure to toxic doses of vitamin D

Table 1. Follow-up the laboratory findings and treatment of the case

Follow-up days	5	17	21	30	38	64	73	105
Calcium (mg/dL) (8.9-10.8)	10.7	11.3	11.7	11.1	11	10.1	11.2	10.1
Ionized calcium (mmol/L) (1-1.3)	1.52		1.57	1.56	1.44	1.4	1.49	1.28
Phosphorus (mg/dL) (4.5-6.7)	2.9	4.7	5.3	4.6	4	4.4	4.7	7.6
Parathormone (pg/mL) (11-67)		<2.5	<2.5		<2.5	5.1	<2.5	80
25 (OH) vitamin D (ng/mL)		85.3			40.2	25		
Urine Ca/ creatinine			2.89		2.0	1.18	2.7	0.004
Platelet $x10^3$/L (150-400)	498	567					515	590
Troponin I (0-0.06)	0.555	1.741	1.127				0.303	0.11
Renal USG		N			Cryst-alloid	Cryst-alloid		
Treatment	Iv hydration diuretic	1 mg/kg/day prednisolone p.o.	1 mg/kg/day prednisolone p.o.	1 mg/kg/day prednisolone p.o.	1 mg/kg/day prednisolone p.o.	1 mg/kg/day prednisolone p.o.	1 mg/day alendronate p.o.	Stop

in this case report was in the last 40 days of pregnancy, unlike in our case.

Vitamin D intoxication in infants is not very common and has generally been reported due to high-dose vitamin D intake[9]. Complications due to maternal high-dose vitamin D intake during pregnancy have been reported very rarely[8,10]. In our case, troponin I elevation, hypoxic-ischemic encephalopathy (HIE) and platelet elevation were also observed. In our case, oral alendronate treatment was given and normocalcemia was achieved. In the literature, another patient with transient hypercalcemia due to maternal high-dose vitamin D intake was reported[10]. In recent years, it has been observed that physicians are more interested in possible problems related to vitamin D deficiency during pregnancy[2]. It has been reported that vitamin D deficiency may be associated with problems such as preeclampsia, gestational diabetes mellitus, postpartum depression, preterm birth, and low birth weight in the literature[1,2]. However, excessive and inappropriate doses of vitamin D may cause severe hypercalcemia, which is a life-threatening complication in the neonatal period[8]. In this article, we discuss a case of hypercalcemia due to maternal high dose vitamin D intake in the last trimester of pregnancy and a newborn with HIE, thrombocytosis, and troponin I elevation. Our case is presented to draw attention to the negative effects of maternal high dose vitamin D intake during pregnancy, to prevent its random use, and to emphasize the importance of questioning the history of prenatal/postnatal maternal vitamin D intake in the etiology of hypercalcemia in the neonatal period.

Ethics

Informed Consent: Written informed consent was obtained from the parents of the patient.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.K.K., M.K., Concept: G.K.K., S.Ç., Design: S.Ç., Data Collection or Processing: Ş.S.E., G.K.K, M.K., S.Ç., Analysis or Interpretation: Ş.S.E., S.Ç., Literature Search: G.K.K., Writing: G.K.K.

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References

1. Perez-Lopez FR, Pasupuleti V, Mezones-Holguin E, Benites-Zapata VA, Thota P, Deshpande A, et al. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analyses of randomized controlled trials. Fertil Steril 2015;103:1278-88.e4. doi: 10.1016/j.fertnstert.2015.02.019.

2. Wei SQ. Vitamin D and pregnancy outcomes. Curr Opin Obstet Gynecol 2014;26:438-47.
3. Ergur AT, Merih Berberoglu M, Atasay B, Şıklar Z, Bilir P, Arsan S, et al. Vitamin d deficiency in Turkish mothers and their neonates and in women of reproductive Age. J Clin Res Pediatr Endocrinol 2009;1:266-9.
4. Karras SN, Wagner CL, Castracane VD. Understanding vitamin D metabolism in pregnancy: from physiology to pathophysiology and clinical outcomes. Metabolism 2018;86:112-23.
5. Hashemipour S, Ziaee A, Javadi A, Movahed F, Elmizadeh K, Javadi EH, et al. Effect of treatment of vitamin D deficiency and insufficiency during pregnancy on fetal growth indices and maternal weight gain: a randomized clinical trial. Eur J Obstet Gynecol Reprod Biol 2014;172:15-9.
6. Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr 2004;80(Suppl 6):1752S-8S. doi: 10.1093/ajcn/80.6.1752S.
7. Saadi HF, Dawodu A, Afandi B, Zayed R, Benedict S, Nagelkerke N, et al. Effect of combined maternal and infant vitamin D supplementation on vitamin D status of exclusively breastfed infants. Matern Child Nutr 2009;5:25-32.
8. Altunhan H, Annagur A, Konak M, Ors R, Bekdas M. A severe neonatal hypercalcemia case due to maternal high dose vitamin D usage. Acta Med Anatol 2013;1:33-4.
9. Ketha H, Wadams H, Lteif A, Singh RJ. Iatrogenic vitamin D toxicity in an infant-a case report and review of literature. J Steroid Biochem Mol Biol 2015;148:14-8.
10. Reynolds A, O'Connell SM, Kenny LC, Dempsey E. Transient neonatal hypercalcaemia secondary to excess maternal vitamin D intake: too much of a good thing. BMJ Case Rep 2017;2017:bcr2016219043. doi:10.1136/bcr-2016-219043.