



SCIENTIFIC LETTER

A neonatal hypocalcaemia due to maternal vitamin D deficiency. Reviewing supplementation[☆]

Hipocalcemia neonatal precoz por déficit de vitamina D materna. Replantando la suplementación

Dear Editor:

Neonatal hypocalcaemia is a common and potentially severe metabolic disorder of variable aetiology. Vitamin D deficiency (VDD) has been described as a cause of neonatal late-onset hypocalcaemia (NLOH). We describe our experience with 2 cases of neonatal early-onset hypocalcaemia (NEOH) associated with neonatal and maternal VDD.

Case 1: newborn girl that developed pathologic tremors at 40h post birth. The mother was of European ascent exposed to sunlight less than 30 min a day. The patient was born in March at 38 weeks of gestation with a birth weight 3590 g in an uncomplicated vaginal delivery. Testing found serum levels of ionized calcium of 4.2 mg/dL, total calcium of 8.1 mg/dL and vitamin D of 14 ng/mL. The infant was given calcium gluconate 10% orally at a dose of 2 mL/kg/day, which improved the clinical manifestations. Testing in the mother found levels of vitamin D of 13 ng/mL and of parathyroid hormone (PTH) of 82.8 pg/mL (15–65 pg/mL).

Case 2: newborn boy that exhibited hypotonia and lethargy at 48 h post birth. The mother was of Arabic ancestry with no exposure to sunlight. The boy was born in February in an uncomplicated delivery at 40 weeks of gestation, with a birth weight of 3180 g. He had serum levels of ionized calcium of 3.27 mg/dL, total calcium of 8.2 mg/dL and vitamin D of 7.1 ng/mL. Calcium gluconate 10% was administered to the patient by the oral route at a dose of 2 mL/kg/day, which improved the clinical manifestations. The mother had serum levels of vitamin D of 4.2 ng/mL, of PTH of 57.9 pg/mL, of total calcium of 8 mg/dL and of phosphorus of 2.5 mg/dL.

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Table 1 Causes of neonatal hypocalcaemia.^a

Neonatal early-onset hypocalcaemia	Neonatal late-onset hypocalcaemia
Preterm birth	Vitamin D deficiency ^b
Intrauterine growth restriction	Hypoparathyroidism
Hypomagnesaemia	Maternal hyperparathyroidism
Hyperbilirubinaemia	Calcium malabsorption
Toxaemia	Diuretic drugs
Perinatal asphyxia	Alkalosis
Maternal type 1 diabetes	Hypomagnesaemia
Maternal hyperparathyroidism	Hyperphosphataemia
Anticonvulsant drugs	Citrate in transfusions (chelating agent)
	Phototherapy

^a Neonatal hypocalcaemia: serum total calcium <8 mg/dL (2 mmol/L) or ionized calcium <4.4 mg/dL (1.1 mmol/L), in term neonates and preterm neonates with birth weights greater than 1500 g, and total calcium <7 mg/dL (1.75 mmol/L) or ionised calcium <4 mg/dL (1 mmol/L) in very low birth weight neonates or neonates weighing <1500 g.

^b Vitamin D level: normal (>30 mg/mL), insufficient (15–30 mg/mL) deficient (<15 mg/mL).

Both mothers resided in Teruel (latitude, 40.25°) and had a skin phototype of 1–2 in the Fitzpatrick scale, a low level of physical activity (took some walks each week) and a body mass index under 30 kg/m², and neither was taking vitamin D. Both mothers were treated successfully with calcifediol supplementation.

Tremors are the most frequent paroxysmal manifestations in the neonatal period, and hypotonia and lethargy are nonspecific symptoms found in neonatal metabolic disorders. They must be assessed as early warning signs of disorders like hypocalcaemia and VDD.¹

The main symptoms of neonatal hypocalcaemia are agitation, tremors, lethargy, seizures, changes in muscle tone, stridor or prolongation of the QTc interval (>0.4 ms). A distinction is made between NEOH (the first 3–4 days of life) and NLOH (the next 5–10 days) (Table 1). Historically, vitamin D deficiency has not been considered a cause of NEOH. The evidence shows a probable association between ethnicity, maternal vitamin D levels and neonatal serum calcium levels,² so that maternal vitamin D levels and neonatal calcium levels may vary depending on the maternal phototype

Table 2 Benefits of isolated vitamin D supplementation found in systematic reviews.

Benefits described by Harvey et al.

Birth weight	Observational	Combined regression coefficient, 5.63 g/10% of maternal vitamin D; 95% CI, 1.11–10.16 g ^a
Birth bone mass	Observational	5 of 8 OSs found a statistically significant association
Neonatal serum calcium levels	Meta-analysis	DM, 0.05 mmol/L; 95% CI, 0.02–0.05 mmol/L ^a

Benefits described by Palacios et al.

Preeclampsia	Meta-analysis	RR, 0.48; 95% CI, 0.30–0.79; 4 RCTs ^a
Gestational diabetes	Meta-analysis	RR, 0.51; 95% CI, 0.27–0.97; 4 RCTs ^a
Low birth weight	Meta-analysis	RR, 0.55; 95% CI, 0.35–0.87; 5 RCTs ^a
Severe postpartum haemorrhage	Meta-analysis	RR, 0.68; 95% CI, 0.51–0.91; 1 RCT ^a
Preterm birth (< 37 WG)	Meta-analysis	RR, 0.66; 95% CI, 0.34–1.30; 7 RCTs

CI, confidence interval; DM, difference of means; OS, observational study; RCT, randomised clinical trial; RR, relative risk; WG, weeks of gestation.

^a Statistically significant.

or cultural factors, and previous data suggest that higher supplementation doses may have a positive impact on the infant, including on calcium levels (Table 2).³

In Spain, one study found that even with multivitamin supplementation including 200 IU/day of vitamin D, 63% of pregnant women have insufficient vitamin D levels and 26% deficient levels.⁴ Another study found levels under 20 ng/mL in 64.4% of mothers and 41.3% of neonates and identified multiple gestation and non-European ethnicity as risk factors for hypovitaminosis D, and maternal supplementation, physical activity and sunlight exposure as protective factors.⁵ Although VDD is very prevalent and underdiagnosed, the authors of systematic reviews with meta-analysis have been cautious in recommending isolated vitamin D supplementation during pregnancy, as the potential relationship of this practice with preterm birth has not been well established, although the relative risk is less than 1 and not statistically significant (Table 2).⁶

Given the above, and taking into account that the immigrant population in Spain is growing, we recommend suspecting VDD as a possible cause of neonatal hypocalcaemia, whether of early or late onset, routine screening of pregnant women for VDD and isolated vitamin D supplementation on a case-by-case basis based on the results, as the potential benefits to pregnant women and infants seems to outweigh the risks.

References

- Collins M, Young M. Benign neonatal shudders, shivers, jitteriness, or tremors: early signs of vitamin D deficiency. *Pediatrics*. 2017;140:e20160719.
- Thomas TC, Smith JM, White PC, Adhikari S. Transient neonatal hypocalcemia: presentation and outcomes. *Pediatrics*. 2012;129:1461–7.
- Harvey NC, Holroyd C, Ntani G, Javaid K, Cooper P, Moon R, et al. Vitamin D supplementation in pregnancy: a systematic review. *Health Technol Assess*. 2014;18:1–190.
- De la Calle M, García S, Duque M, Bartha JL. Vitamin D concentrations are decreased in singleton and twin pregnancies. *Med Clin (Barc)*. 2016;147:371–2.
- Blarduni E, Arrospe A, Galar M, Castaño L, Mar J, Grupo GOI-VIDE. Factores asociados a la prevalencia de hipovitaminosis D en mujeres embarazadas y sus recién nacidos. *An Pediatr (Barc)*. 2019;91:96–104.
- Palacios C, Kostiuk LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. *Cochrane Database Syst Rev*. 2019;7:CD008873.

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