CASE REPORT

Transient neonatal hypercalcaemia secondary to excess maternal vitamin D intake: too much of a good thing

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SUMMARY

We report a case of transient neonatal hypercalcaemia secondary to excess maternal vitamin D intake in pregnancy. Vitamin D insufficiency and deficiency in pregnancy are associated with adverse pregnancy outcomes, but there is no definite benefit to supplementation. The Royal College of Obstetrics and Gynaecology recommends routine supplementation with vitamin D₃ 400 IU/day, but higher dose preparations usually recommended for the treatment of vitamin D deficiency are readily available over the counter. This case highlights the risks of excess supplementation, especially at higher doses and in women without evidence of vitamin D deficiency. The amount used in this case was at the upper end of the generally accepted safe dose range, but still less than that commonly recognised to cause problems. Neonatal hypercalcaemia is a potentially serious condition. The current local or national recommendations for vitamin D supplementation and the possible adverse effects of excess vitamin D consumption should be clearly communicated to pregnant women.

BACKGROUND

Following recent focus on vitamin D supplementation in infancy, routine supplementation for the first 2 years of life is advocated. However, the role of maternal vitamin D supplementation in pregnancy is still uncertain.

During a consultation, over-the-counter (OTC) medications are easily overlooked by both the patients and the clinicians. In some cases, a thorough medication history will obviate the need for further investigation.

CASE PRESENTATION

A baby girl was born to Caucasian parents at 39 weeks' gestational age following an uncomplicated pregnancy. There was no maternal history of any significant medical illness or family history of abnormal calcium metabolism. She was exclusively breast fed.

On routine newborn examination, the baby was found to have a cystic mass protruding from the vagina. A surgical opinion was requested and she was provisionally listed to have the lesion surgically removed. On day 5 of life, she had a number of routine preoperative investigations performed. She was incidentally found to have hypercalcaemia. Her total serum calcium was 3.09 mmol/L (1.9–2.6),

with an ionised calcium level of 1.47 mmol/L (1–1.5). Her 25-hydroxyvitamin D concentration was at the upper end of the normal range (73 nmol/L) (table 1). Her parathyroid hormone level was appropriately suppressed (5 ng/L). The paravaginal mass spontaneously ruptured and no intervention was required.

Subsequent enquiry revealed a history of excessive maternal vitamin D intake. From several months prior to conception, the patient's mother had been taking two supplements: one multivitamin capsule containing 1000 IU vitamin D₃ three times per day and one 1000 IU vitamin D₃ oral spray once per day. The total daily vitamin D₃ intake was 4000 IU. While the mother's own total serum calcium (2.38 mmol/L) concentration was normal, her 25-OH vitamin D was very elevated (127 nmol/L) and her parathyroid hormone (PTH) level was appropriately suppressed (13 ng/L) (table 2).

OUTCOME AND FOLLOW-UP

Despite the elevated total serum calcium, the baby remained clinically well. A renal ultrasound was performed on day 1 of life and again on day 5 of life. There was no evidence of nephrocalcinosis. Routine vitamin D supplementation was withheld. The infant continued to breast feed exclusively. The total serum calcium level was monitored and found to be elevated on several more occasions, but dropped to the normal range within 2 weeks.

DISCUSSION

The differential diagnosis of hypercalcaemia in the newborn is broad and includes conditions with elevated PTH (neonatal hyperparathyroidism), normal PTH (familial hypocalciuric hypercalcaemia) and suppressed PTH (malignancy, subcutaneous fat necrosis and Williams syndrome).^{1,2} In this case, the biochemical profile consisted of elevated total serum calcium, hypercalciuria and appropriately suppressed PTH. Taken together with a history of high maternal vitamin D intake, this profile allowed us to make a presumptive diagnosis of neonatal hypercalcaemia secondary to excess maternal vitamin D intake in pregnancy. Since the baby's calcium level returned to the normal range within 2 weeks of birth, the need for further investigation was avoided.

The role of vitamin D supplementation in pregnancy remains uncertain. Antenatal vitamin

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Table 1 Initial neonatal laboratory test results

Test	Result	Reference range
Total calcium	3.09 mmol/L	(1.9–2.6)
Ionised calcium	1.47 mmol/L	(1–1.5)
Albumin	40 g/dL	(35–52)
Phosphate	1.96 mmol/L	(1.25–2.25)
Magnesium	0.73 mmol/L	(0.7–1)
Alkaline phosphatase	318 U/L	(48–406)
Parathyroid hormone	5 ng/L	(15–65)
25-hydroxyvitamin D	73 nmol/L	(50–75 nmol/L: adequate)
Urine calcium/creatinine ratio	5.6 mmol/mmol	(<2.42 mmol/mmol) ¹⁹
Urine phosphate	None detected	

D deficiency is common and has been associated with several adverse maternal and infant outcomes, including pre-eclampsia, low birth weight and recurrent childhood wheeze.^{3–5} In severe cases, neonatal hypocalcaemia can result in seizures, cardiomyopathy or tetany.⁶ However, there are currently no data from randomised controlled trials to show a benefit from routine vitamin D supplementation. A recent Cochrane review concluded that there is insufficient evidence to support the routine use of antenatal vitamin D.⁷ The American Congress of Obstetricians and Gynecologists suggests that clinicians may check vitamin D levels in women at increased risk and should treat only in cases of proven hypovitaminosis D.⁸ Conversely, the Royal College of Obstetrics and Gynaecology recommends routine supplementation with vitamin D₃ 400 IU/day and at least 1000 IU/day for women at increased risk of deficiency.⁹

Despite the absence of definitive evidence to support the routine use of vitamin D in pregnancy, some women will elect to take supplements. Without proven vitamin D deficiency or monitoring of their vitamin D levels, these women and their infants may be at risk of hypervitaminosis D. Therefore, the risks of vitamin D excess should be clearly communicated. This is especially important because higher dose preparations usually recommended for the treatment of vitamin D deficiency are readily available OTC.

There are limited data to suggest what dose is the safe upper limit for routine vitamin D supplementation in pregnancy. In healthy non-pregnant adults, there is evidence that vitamin D₃ 10 000 IU/day is well tolerated for periods of at least 6 months.¹⁰ However, it is not certain that similar doses would be tolerated in pregnancy or that the absence of toxicity in the mother precludes toxicity in the fetus. The possibility of a hypercalcaemia-independent teratogenic effect of vitamin D was raised by animal studies, but has not been found in humans.¹¹

Table 2 Maternal laboratory test results

Test	Result	Reference range
Total calcium	2.38 mmol/L	(2.1–2.66)
Albumin	41 g/dL	(35–52)
Phosphate	1.23 mmol/L	(0.8–1.5)
Magnesium	0.83 mmol/L	(0.7–1)
Alkaline phosphatase	175 U/L	(30–120)
Parathyroid hormone	13 ng/L	(15–65)
25-hydroxyvitamin D	127 nmol/L	(>125 nmol/L: excess)
Urine calcium/creatinine ratio	0.26 mmol/mmol	(<0.61 mmol/mmol) ¹⁹
Urine phosphate	14.0 mmol/L	

Patient's perspective

"I started acupuncture treatment... as I had read that this boosts fertility. [I was advised] to start taking [supplements]. [Later] I started IVF treatment. After two unsuccessful treatments, I had a... confirmed pregnancy. [I switched to] supplements designed for each trimester. [We had a] noisy, cute, healthy and beautiful baby. [The consultant] found a cyst protruding from the vagina. They took bloods in case she needed surgery. The high calcium level was highlighted at this time. The cyst was decreasing in size. They were reluctant to release [her] from their care due to the high level of vitamin D in her blood. The high calcium level was diagnosed [as due to my] level of high vitamin D. [The doctors kept] a watchful eye on [my daughter] and her bloods for a couple of weeks and months. My daughter is now 9 months and I have not taken any further supplements and continue to breastfeed. [It was] an unsure and worrying time."

Few trials have rigorously reported rates of teratogenesis, but the evidence that exists is reassuring. Doses of 200 000 IU/day vitamin D₂ used in women with hypoparathyroidism have apparently not resulted in congenital anomalies.¹² However, the risk of neonatal hypercalcaemia is distinct from the risk of teratogenesis. In a review of vitamin D safety published in 2011, Roth¹³ wrote: 'prospective trials published to date have not adequately reported maternal or fetal/infant [Ca] ranges or risks of hypercalcaemia in normal pregnancies'.

Most experts agree that vitamin D₃ 1000–2000 IU/day is safe in the setting of proven deficiency.⁹ However, there is evidence that some women may not have an adequate response to this dose range and higher daily requirements have been suggested.¹⁴ In 2010, the National Academy of Medicine (USA) stated that vitamin D₃ 4000 IU/day is the tolerable upper intake limit during pregnancy and lactation.¹⁵ Although the dose used in this case (4000 IU/day) is significantly greater than the usual prophylactic dose, it is still less than that commonly recognised to cause problems. In a trial published in 2011, 169 women with a baseline 25-hydroxyvitamin D level <40 nmol/L were randomised to receive vitamin D₃ 4000 IU/day from early in the second trimester until delivery.¹⁶ Three developed hypervitaminosis D defined as a 25-hydroxyvitamin D level greater than 90 nmol/L.

In this case, hypercalcaemia was an incidental finding. Maternal hypervitaminosis D led to neonatal hypercalcaemia, but the mother's own calcium levels were not elevated. For the infant, hypercalcaemia occurred at a vitamin D level not normally considered excessive. The ionised calcium level stayed just within the normal range and the infant was asymptomatic. However, neonatal hypercalcaemia is a potentially serious condition. Severe cases may present with seizures, bradycardia, hypertension, vomiting, hypotonia, polyuria or failure to thrive.¹⁷ Hypervitaminosis D can cause nephrocalcinosis and occasionally soft tissue calcification. This infant's urinary calcium excretion was elevated, suggesting an increased risk of renal complications.

This baby's initial presentation with a mass protruding from the vagina was not thought to be related to her hypercalcaemia. The differential diagnosis of a congenital interlabial mass includes lesions arising from the vaginal wall (Skene glands, Bartholin's cysts, sarcoma), above the hymen (hydrocolpos, hydrometrocolpos) and from the urological system (prolapsed ureterocele). Early spontaneous regression of paraurethral cysts caused by Skene's duct obstruction has previously been reported.¹⁸

Learning points

- ▶ Given its prevalence and deleterious effects, hypovitaminosis D in pregnancy constitutes an important public health issue.
- ▶ Based on the currently available evidence, it is unclear which mothers should receive supplementation and what dose they should be given.
- ▶ This case highlights the risks of excess vitamin D supplementation, especially at higher doses and in women without evidence of deficiency.
- ▶ The current local or national recommendations for vitamin D supplementation and the possible adverse effects of excess vitamin D consumption should be clearly communicated to pregnant women.

Contributors ED conceived the report and revised it critically. AR drafted the report. SMOG and LCK reviewed the report and revised it critically. All authors approved the final version and agree to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

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