Subcutaneous Infusion of rhPTH1-34 During Pregnancy and Nursing in a Woman With Autosomal Dominant Hypoparathyroidism 1

Dorothy Shulman,1,2

1University of South Florida Diabetes and Endocrinology Center, USF Morsani College of Medicine, Tampa, FL 33612, USA
Correspondence: Dorothy Shulman, MD, USF Diabetes and Endocrinology Center, USF Morsani College of Medicine, 12901 Bruce B. Downs Blvd., Tampa, FL 33612, USA. Email: dshulman@usf.edu.

Abstract

We report a successful pregnancy in a young woman with autosomal dominant hypoparathyroidism type 1 (ADH1) due to an activating mutation of the calcium sensing receptor (CASR) (c.2519C>T; p.Ala840Val) who was treated with recombinant human parathyroid hormone (rhPTH)1-34 delivered via continuous subcutaneous infusion using an OmniPod pump. She experienced no tetany or hospitalizations during the pregnancy. Serum calcium levels ranged from 7.2 to 9.8 mg/dL. Due to mild preeclampsia, her infant was delivered at 37 weeks. There were no physical anomalies. The patient continued pump therapy while nursing her daughter, who was ultimately confirmed to have the same CASR mutation. Breastfeeding appeared to protect the infant from significant hypocalcemia without the need for calcium or calcitriol supplementation until weaning at a year of age. A role for parathyroid hormone-related protein (PTHrP) is suggested.

Key Words: autosomal dominant hypoparathyroidism 1, pregnancy, rhPTH1-34

Abbreviations: ADH1, autosomal dominant hypoparathyroidism type 1; CASR, calcium sensing receptor; eGFR, estimated glomerular filtration rate; NIH, National Institutes of Health; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related protein; rhPTH, recombinant human parathyroid hormone.

Hypoparathyroidism during pregnancy is rare and is traditionally treated with activated vitamin D metabolites and calcium supplementation to maintain serum calcium levels within the low-normal to mid-normal physiologic range to avoid severe hypocalcemia and hypercalciuria [1]. Miscarriage, fetal skeletal demineralization and fractures, pre-term delivery and low birth weight have been reported [1-4]. Treatment of hypoparathyroidism with recombinant human parathyroid hormone (rhPTH)1-34 is approved in the United States and Europe for individuals with a poor response to traditional therapy; however, its use in pregnancy or during lactation is not recommended [5-8]. rhPTH1-34 (Forteo) is approved by the Food and Drug Administration only for treatment of postmenopausal osteoporosis, though it has been used off-label for treatment of hypoparathyroidism [6, 7]. It is considered Category C in pregnancy; increased skeletal deviations and variations were observed in mouse offspring at doses more than 60 times the equivalent human dose [8]. Breastfeeding is not recommended due to lack of safety data. There is a single case report of a pregnant patient with iatrogenic hypoparathyroidism treated with rhPTH1-34 delivered via continuous subcutaneous infusion [9]; no adverse effects were identified.

We report a successful pregnancy in a young woman with autosomal dominant hypoparathyroidism type 1 (ADH1) due to an activating mutation of the calcium sensing receptor (CASR) (c.2519C>T; p.Ala840Val) who was treated with rhPTH1-34 (Forteo, Lilly, Indianapolis, IN) delivered via continuous subcutaneous infusion using an OmniPod pump (Insulet, Acton, MA). She continued pump therapy while nursing her daughter who was, ultimately, confirmed to have the same CASR mutation. Breastfeeding appeared to protect the infant from significant hypocalcemia until weaning at a year of age.

Case Report

The patient is a 26-year-old Caucasian female who was diagnosed with hypocalcemia (7 mg/dL) and hypoparathyroidism at 6 months of age after a paternal aunt with ADH1 suggested that she be tested. Father, paternal grandmother, and paternal great aunts are affected. She was treated with calcitriol and calcium, and during childhood had recurrent episodes of laryngospasm due to hypocalcemia, periodically requiring hospitalization. Significant nephrocalcinosis was present on renal ultrasound. At age 10 years she entered a long-term study at the National Institutes of Health (NIH) receiving twice daily injections of PTH1-34 prepared at the NIH research pharmacy [10]. Her clinical status stabilized although some hypercalciuria persisted. She also participated in a 6-month trial using the OmniPod pump to deliver PTH1-34, which resulted in normalization of serum calcium and 24-hour urinary calcium excretion during the study [11]. The NIH program closed when the patient was 17 years of age and she was...
transitioned to a commercial source of PTH\textsuperscript{1-34} (Forteo) delivered via an OmniPod pump. The PTH\textsuperscript{1-34} dose was initially 15 mcg daily delivered as a single basal infusion rate over 24 hours and was gradually increased over the subsequent 7 years to 26 mcg/day with the goal of keeping serum calcium levels between 7.5 and 8.5 mg/dL to avoid hypercalciuria. She also took vitamin D\textsubscript{3} 1000 international units (IU) daily, magnesium oxide 400 mg twice daily, and calcium carbonate 0 to 3 g orally depending on serum calcium. Although there were mild episodes of symptomatic hypocalcemia, usually associated with menses or upper respiratory infections, clinical status was stable and 24-hour urine calcium excretion remained within the normal range, as did renal function. She graduated from college, began working full time as a teacher, and married. Renal ultrasound was unchanged revealing severe medullary nephrocalcinosis. Bone mineral densitometry was normal in the spine and hip, but osteopenic in the forearm in the year prior to pregnancy (lumbar spine 1.44 g/cm\textsuperscript{2}; z = 1.9; total left femur 1.006 g/cm\textsuperscript{2}; z = −0.1; z = −0.8; left forearm 0.714 g/cm\textsuperscript{2}; z = −1.9). Planning a pregnancy, she wanted to stay on PTH\textsuperscript{1-34} via pump and her obstetrician agreed.

Conception occurred without difficulty and was confirmed at 4.5 weeks gestation. Serum calcium goal was 8 to 9 mg/dL so as not to restrict calcium in a fetus with a 50% chance of being unaffected by the CASR mutation. Chronic maternal hypocalcemia could result in hyperparathyroidism in an unaffected fetus with resultant bone demineralization and fractures. Subcutaneous rhPTH\textsuperscript{1-34} infusion at the start of pregnancy was 30 mcg/daily delivered as a single basal infusion rate and was decreased transiently to 27 mcg in the first month due to calcium level rising to 9.8 mg/dL. It was subsequently increased again to 28 mcg for the remainder of the pregnancy. Calcium levels were assessed as frequently as twice weekly and calcium supplementation was given intermittently up to 2 grams daily if calcium fell below 8 mg/dL. On 3 occasions the calcium dipped below 7.5 mg/dL and a 12.5-mcg rhPTH\textsuperscript{1-34} bolus infusion was delivered via the pump in addition to the calcium supplementation. When the calcium rose above 9.5 mg/dL on 2 occasions, the pump basal infusion rate was lowered by 50% for 3 to 4 hours. There were no emergency room visits or hospitalizations for tetany. Calcium remained between 7.2 and 9.8 mg/dL. (Fig. 1). One 24-hour urine specimen was collected at 12 weeks gestation which revealed an elevated urine calcium/creatinine ratio of 0.47 (normal laboratory value [nl] < 0.26) with urine calcium 640 mg/24 hours (nl < 300 mg) with a concomitant serum calcium of 8.1 mg/dL. Estimated glomerular filtration rate (eGFR) was normal at 109 ng/mL/min/1.73m\textsuperscript{2}.

At 4 months gestation 25-hydroxyvitamin D was 34 ng/mL (nl 30-100 ng/dL), 1,25 hydroxyvitamin D was 115 pg/mL (nl 18-72 pg/mL). High-resolution fetal ultrasound evaluations at 19 weeks, 28 weeks, and 34 weeks showed excellent fetal growth with no structural abnormalities. At 36 weeks the patient developed hypertension and preeclampsia. At 37 weeks she received betamethasone on 2 consecutive days and labor was induced. Due to failure to progress, a cesarian section was performed. A vigorous female infant weighed 3560 gm, head circumference 34 cm, length 51 cm. The infant’s Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. At 7 hours of life the infant was noted to have mild subcostal retractions and was transferred to the newborn intensive care unit. She received intravenous fluids and was placed on a positive pressure mask and 21% O\textsubscript{2} overnight. Impression was transient tachypnea of the newborn. Clinical condition improved by the following day, and she began nursing well. Hearing screen was normal. Serum calcium on day 2 of life was 7.1 mg/dL and rose to 7.2 mg/dL later the same day. On the following day, calcium was 7.6 mg/dL (nl 8.2-10 mg/dL), magnesium level was 1.8 mg/dL (nl 1.8-2.4 mg/dL), and 25-hydroxyvitamin D was 48.7 ng/dL. Calcium carbonate 100 mg orally twice daily was started as a precaution so that she could be discharged home. The infant was examined at the University of South Florida Pediatric Endocrine Clinic at 7 days of age. She was an alert term female infant weighing 3430 g.

Figure 1. Serum calcium levels in a woman with ADH1 during pregnancy and during the first year postpartum while nursing. Patient was treated with PTH\textsuperscript{1-34} via continuous subcutaneous insulin infusion with an OmniPod pump during pregnancy and until 8 months postpartum when her therapy switched to calcitriol. She began weaning her infant at 11 months of age.
Her calcium level was 9.3 mg/dL and PTH < 1 pg/mL (nl 12-65 pg/mL). Calcium supplementation was continued until 21 days when the serum calcium was documented at 9.6 mg/dL; then calcium supplementation was discontinued. Vitamin D3 400 IU daily was added to her diet at 2 months of age. Serum 1,25-hydroxyvitamin D at 2 months was 63 pg/mL. In the first year of life the baby thrived on breast milk with solid food supplementation initiated at 6 months. Serum calcium and PTH levels in the infant are shown in Fig. 2. Serum calcium remained in the low-normal range with low PTH levels. Serum PTHrP (PTH-related protein) levels were measured 3 times during the first year and once shortly after weaning at 1 year (Quest Diagnostics, San Juan Capistrano, CA) (Fig. 2). When the infant was nearing 8 months of age, the mother’s therapy switched to calcitriol as her new insurance would not cover rhPTH1-34. She began weaning at 11 months. At 1 year of age, following immunizations, the infant developed fever, poor appetite, and had a brief 1-minute seizure. She was taken to local emergency room. Calcium level was 7.6 mg/dL, ionized calcium was 0.9 mmol/L (nl 1.24-1.3 mmol/L). She was admitted for observation due to poor oral intake. The impression was a febrile seizure. She was started on intravenous fluids with oral calcium supplementation. Calcium level rose to 7.6 mg/dL after 48 hours; oral intake improved. Calcitriol 0.25 mcg orally daily was added, and calcium rose to 7.9 mg/dL, allowing her to be discharged. One week later, her serum calcium rose to 8.6 mg/dL, phosphorus was 7.7 mg/dL (nl 4.8 mg/dL), and PTHrP was 12 pg/mL (nl 14-27 pg/mL), significantly lower than previous levels. Genetic testing (GeneDx, Gaithersburg, MD) for CASR mutation was positive for the c.2519C>T (p.Ala840Val) heterozygous mutation identified in other affected family members. A renal ultrasound was negative for nephrocalcinosis. Growth and development are normal at 1.5 years of age.

During lactation the mother’s rhPTH1-34 dose decreased slightly and she required very little calcium supplementation. rhPTH1-34 dose increased again when her menses resumed and the frequency of nursing decreased. When mother was switched to calcitriol therapy, calcium 1 g daily was required. Switching to calcitriol had no noticeable effect on the baby’s serum calcium level. The mother’s eGFR has remained normal following the pregnancy.

**Discussion**

We describe a successful pregnancy exposed to continuous subcutaneous therapy with rhPTH1-34. The total daily doses were only modestly above those recommended for treatment of osteoporosis (20 mcg daily). Calcium levels were relatively stable with no episodes of tetany. Hypercalcuria was documented on a 24-hour urine assessed at 12 weeks gestation; however, this was anticipated, as serum calcium levels were averaging above the prepregnancy target of 7.5 to 8.5 mg/dL where, historically, hypercalcuria had been minimized. Higher serum calcium levels were targeted during the pregnancy to minimize relative hypocalcemia in a fetus unaffected by the CASR mutation. Such an infant could develop in utero hyperparathyroidism and severe bone demineralization if exposed to chronic hypocalcemia. A relative increase in urinary calcium excretion is a feature of normal pregnancy and may even be associated with an increased risk of kidney stone formation [12, 13]. No major adjustment of the rhPTH1-34 infusion rate was required throughout the pregnancy, which was also an observation of Ilany et al [9]. During lactation there was a modest decrease in rhPTH1-34 dose and our patient required little calcium supplementation. Sweeney et al reported a 34-year-old pregnant woman with ADH1 in whom an initial calcitriol dose of 0.75 mcg daily was actually discontinued at 28 weeks gestation due to hypercalcemia [14]. The infant was delivered early at 30 weeks due to preeclampsia. Calcitriol 0.25 mcg was resumed at delivery due to hypocalcemia but

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Serum calcium, PTH, and PTHrP levels during the first year of life in an infant with ADH1. Major milk source was breast milk until 11 months of age. Calcium levels remained in the low-normal range (nl 8.2-10 mg/dL), despite low PTH levels (nl 12-65 pg/mL) without calcium or calcitriol supplementation until 1 year of age. Serum PTHrP levels appeared to be in the mid-normal range (nl 14-27 pg/mL) during nursing and dropped after weaning. A hypocalcemic episode following fever and poor oral intake after vaccinations prompted initiation of calcium and calcitriol supplementation.
again had to be discontinued after 1 month of nursing due to recurrent hypercalcemia. The authors attributed these changes in calcitriol requirement to PTHrP secretion by the placenta during the pregnancy and breasts during lactation. A 38-year-old woman with ADH1 was reported to have stable levels of serum calcium during pregnancy managed with calcitriol and calcium supplementation. Three weeks into lactation she, too, developed hypercalcemia requiring a reduction in calcitriol dose [3]. Calcium and calcitriol requirements appear to be reduced during lactation in women with ADH1 and other hypoparathyroidism likely due to increased PTHrP [1-3]. The magnitude of change in therapy observed during pregnancy and lactation in these few cases is variable illustrating the need for frequent monitoring and individualization of therapy. Our patient developed preeclampsia at 37 weeks. Although the patient of Sweeney et al developed preeclampsia [14], it is not specifically reported as a complication of hypoparathyroid pregnancies [1-3]. Bjornsdottir et al did observe an increased risk of preeclampsia in a Norwegian registry of hypoparathyroid women relative to controls; however, after controlling for diabetes, chronic kidney disease, and maternal age, the incidence of preeclampsia was no longer different [4]. Preeclampsia occurs in 3% to 5% of all pregnancies [15]. Chronic renal disease is a risk factor. It is unclear if our patient’s diffuse medullary nephrocalcinosis put her at increased risk.

Intrauterine growth and organ development in our patient’s infant as assessed by fetal ultrasound and postnatal physical examinations during the first year of life were normal. Of interest is that the female infant, ultimately proven to have an activating mutation of CASR appeared to be protected from severe hypocalcemia during the first year of life by mother’s breast milk. This potentially may be explained by calcium, vitamin D and its metabolites in breast milk, under the influence of maternal mammary PTHrP [16, 17]. PTHrP is synthesized by many fetal and adult tissues (cartilage, bone, muscle, skin, breast, intestines, parathyroid, pancreas, pituitary, placenta, and central nervous system) and plays a crucial role in chondrocyte differentiation and maturation, mammary gland and tooth formation, and epidermal and hair follicle growth in the fetus [17, 18]. During lactation, PTHrP is released on the stimulus of sucking and secreted into the milk in quantities that are 10,000 times as high as those in serum [19, 20]. PTHrP is thought to play a role in maintaining a positive calcium gradient in breast milk. PTHrP is synthesized locally and acts primarily as a paracrine or autocrine messenger. Its production is constitutive and is controlled at the point of expression of its encoding gene. It is indispensable for a successful pregnancy and fetal development, as embryonic gene deletion is lethal in mammals [17]. The association of elevated circulating levels of PTHrP and hypercalcemia in some malignancies provides evidence for a humoral role in elevating serum calcium. In this setting PTHrP activates the PTH receptor raising calcium by increasing bone resorption and renal tubular resorption of calcium.

Serum PTHrP levels in the infant of our patient were in the mid-normal range during the first year while nursing. A single sample drawn after weaning showed her level had dropped significantly. The source of the infant’s serum PTHrP concentrations, and the cause for the apparent drop in the level following weaning are not clear. One may speculate that suckling stimulated endogenous PTHrP production in the infant, or that there possibly was some intestinal absorption from breast milk. A direct role for PTHrP in maintaining relative eucalcaemia in the presence of PTH deficiency in the infant is also unknown.

In summary, we report a successful pregnancy in a young woman with hypoparathyroidism due to ADH1 treated with continuous subcutaneous infusion of rhPTH 1-34. While most hypoparathyroid pregnancies are able to be managed with activated vitamin D and calcium, this single case report provides further evidence that this therapy may be carried out safely in individuals who have been treated successfully with PTH and wish to remain on it. Breastfeeding may be protective against hypocalcemia in infants with ADH1.

Financial Support
There was no funding supporting the writing of this paper.

Disclosures
The author has no conflicts of interest to report relative to this case report or its subject matter.

Data Availability
Some or all data generated or analyzed in this study are included in this published article or in the data repositories listed in References.

References
1. Ali DS, Dandurand K, Khan AA. Hypoparathyroidism in pregnancy and lactation: current approach to diagnosis and management. J Clin Med. 2021;10(7):1378-1392. doi:10.3390/jcm10071378
2. Wang J-J, Wang O, Wang Y-B, et al. Changes in serum calcium and treatment of hypoparathyroidism during pregnancy and lactation: a single-center case series. J Clin Endocrinol Metab. 2021;106(12):e5054-e5063. doi:10.1210/clinem/dgab530
3. Hatswell BL, Allan CA, Teng J, et al. Management of hypoparathyroidism in pregnancy and lactation- a report of 10 cases. Bone Rep. 2015;3:15-19. doi:10.1016/j.bonr.2015.05.005
4. Bjornsdottir S, Clarke B, Makitie O, et al. Women with chronic hypoparathyroidism have low risk of adverse pregnancy outcomes. J Clin Endocrinol Metab. 2021;106:3312-3319. doi:10.1210/clinem/dgab503
5. Natpara [package insert]. Shire-NPS Pharmaceuticals; 2020.
6. Gafni RL, Collins MT. Hypoparathyroidism. N Engl J Med. 2019;380:1738-1747. doi:10.1056/NEJMcp1800213
7. Bilezikian JP, Brandi ML, Cusano NE, et al. Management of hypoparathyroidism: present and future. J Clin Endocrinol Metab. 2016;101(6):2313-2324. doi:10.1210/jc.2015-3910
8. Forteo [package insert], Eli Lilly & Co; 2002.
9. Ilany J, Vered I, Cohn O. The effect of continuous subcutaneous recombinant PTH (1-34) infusion during pregnancy on calcium homeostasis-a case report. J Gynaecol Endocrinol. 2013;29(9):807-810. doi:10.3109/09513590.2013.813473
10. Winer KK, Kelly A, Johns A, et al. Long term parathyroid hormone 1-34 replacement therapy in children with hypoparathyroidism. J Pediatr. 2018;203:391.e1-399.e1. doi:10.1016/j.jpeds.2018.08.010
11. Winer KK, Fulton KA, Albert PS, Cutler GB Jr. Effects of pump versus twice-daily injection delivery of synthetic parathyroid hormone 1-34 in children with severe congenital hypoparathyroidism. J Pediatr. 2014;165(3):556-563.e1. doi:10.1016/j.jpeds.2014.04.060
12. Maikranz P, Holley JL, Parks JH, Lindheimer MD, Nakagawa Y, Cole FL. Gestational hypercalciuria causes
pathological urine calcium oxalate supersaturations. *Kidney Int*. 1989;36:108-113.

13. Thongprayoon C, Vaughan LE, Chewcharat A, *et al*. Risk of symptomatic kidney stones during and after pregnancy. *Am J Kidney Dis*. 2021;78(3):409-417. doi:10.1053/j.ajkd.2021.01.008

14. Sweeney LL, Malabanan AO, Rosen H. Decreased calcitriol requirement during pregnancy and lactation with a window of increased requirement immediately postpartum. *Endocr Pract*. 2010;16(3):459-462. doi:10.4158/ep099337.cr

15. Fox R, Kitt J, Leeson P, Aye CYL, Lewandowski AJ. Preeclampsia: risk factors, diagnosis, management, and the cardiovascular impact on the offspring. *J Clin Med*. 2019;8(10):1625-1647. doi:10.3390/jcm8101625

16. Bae YJ, Kratzsch J. Vitamin D and calcium in the human breast milk. *Best Pract Res Clin Endocrinol Metab*. 2018;32(1):39-45.

17. Strewler GJ. The physiology of parathyroid hormone-related protein. *N Engl J Med*. 2000;342:177-185. doi:10.1056/NEJM200001203420306

18. Naafs MAB. Parathyroid hormone related peptide (PTHRP): a mini-review. *Endocrinol Metab Int J*. 2017;5(6):321-328.

19. Thiede MA, Rodan GA. Expression of a calcium-mobilizing parathyroid hormone-like peptide in lactating mammary tissue. *Science*. 1988;242(4876):279-280. doi:10.1126/science.3175653

20. Budayr AA, Halloran BP, King JC, Diep D, Nissenson RA, Strewler GJ. High levels of a parathyroid hormone–like protein in milk. *Proc Natl Acad Sci*. 1989;86(18):7183-7185.