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Case Report

Maternal and Fetal Outcome After Long-Term Pamidronate Treatment Before Conception: A Report of Two Cases

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ABSTRACT: The pregnancies of two women with osteogenesis imperfecta who received intravenous pamidronate before conception are reported. The mothers suffered no ill effects. One baby had transient asymptomatic hypocalcemia and one had bilateral talipes equinovarus.

This report documents the pregnancy outcomes of two women with osteogenesis imperfecta (OI), types I and IV, who received intravenous pamidronate as part of an observational trial before conception. Pamidronate was not administered after conception. Other than hyperemesis in one woman, the pregnancies and deliveries were uneventful. Both babies inherited OI from their mothers. The baby with OI type IV also had bilateral talipes equinovarus. Biochemical evaluation of the mothers and babies at 24 h and/or 2 weeks postpartum was normal, apart from one baby with asymptomatic hypocalcemia at 24 h of age that had resolved when next measured on day 11 of life. No biochemistry was available on the second child until 13 days of age. Neither baby had skeletal modeling abnormalities consistent with in utero pamidronate exposure. The lumbar spine (L_1–L_4) areal BMD and anterior to posterior height ratios of lumbar vertebral bodies of both women remained constant during pregnancy. Both the mothers and babies remain well and free of fracture 14 and 16 months postpartum.
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Key words: osteogenesis imperfecta, pamidronate, pregnancy, maternal, fetal, outcome

INTRODUCTION

OSTEOGENESIS IMPERFECTA (OI) is a heritable disorder characterized by frequent fractures, low bone mass, short stature, and skeletal deformities.[1] Cyclical pamidronate therapy has been reported to increase vertebral BMC and muscle strength and to reduce fracture rates and bone pain in children with moderate to severe OI.[1] However, a frequently voiced concern is that pamidronate therapy administered to girls and young women might adversely affect the outcome of subsequent pregnancies.[2,3]

Bisphosphonates have been shown to cross the placenta in both animals and humans.[2,4–7] The administration of bisphosphonates to rats during gestation may lead to symptomatic hypocalcemia in the dams during the later stages of pregnancy, as well as prolongation of parturition and fetal demise.[2,8] Rat studies have also shown that high-dose bisphosphonate therapy during pregnancy can result in shortening of diaphyseal bone, increased diaphyseal trabecular volume, and a reduction in bone marrow volume in the fetus.[2,6] Because of such observations, the use of bisphosphonates during pregnancy is contraindicated, and women of childbearing potential should have a pregnancy test performed before each pamidronate treatment cycle.

Nevertheless, two case reports have been published on pregnant women who received bisphosphonates for malignant hypercalcemia.[9,10] In both cases, the infant was delivered within 2 weeks after the administration of the bisphosphonate and developed hypocalcemia requiring supplemental intravenous calcium.[9,10] In both cases, the authors were unable to ascertain if the neonatal hypocalcemia resulted from the antenatal maternal hypercalcemia or the bisphosphonate therapy.

Bisphosphonates are known to persist in mineralized bone for many years.[11] Therefore, even if use of these drugs is avoided during pregnancy, the fetus might still be exposed to bisphosphonates released from the maternal skeleton if the mother received bisphosphonates before conception.[2,3] It is also conceivable that the suppressed bone turnover caused by residual bisphosphonate effect might cause maternal complications during pregnancy or lactation.

To our knowledge, there is no published information from either animal or human studies on whether long-term pamidronate administration before pregnancy has any of

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TABLE 1. BIOCHEMICAL AND BMD DATA

Subject	Days postpartum	Calcium total (mM)	Calcium ionized (mM)	Phosphate (mM)	Alkaline phosphatase (U/liter)	PTH(39–84) (pM)	aBMD (g/cm^2)	aBMD z score
Case 1 mother	Last treatment visit	2.34	1.26	1.53	93	7	0.890	−1.13
	1	2.16	1.23	1.37	167			
	11	2.25		1.38	112	4.6	0.888	−1.16
Case 1 baby	1	2.22	0.98		292			
	11	2.55			281	3.4	0.157	−1.77
Case 2 mother	Last treatment visit	2.25	1.23	1.17	115	14.4	0.763	−2.29
	13	2.32	1.26	1.40	120	11.2	0.781	−2.14
Case 2 baby	13	2.86		2.22	175	6.3	0.213	0.71

Reference data[12,13]: calcium total: newborn 24–48 h 1.75–3.0 mM; adult 2.10–2.55 mM; calcium ionized: newborn 24–48 h 1.00–1.17 mM, adult 1.12–1.23 mM; phosphate: 1–3 years 1.25–2.10 mM, adult 0.90–1.50 mM; alkaline phosphatase: 1–9 years 145–420 U/liter, adult 50–130 U/liter; PTH(39–84): 2.6–10.0 pM.

these theoretical detrimental effects on mother or child. We present the cases of two women with OI and their children, where the mothers had received intermittent intravenous pamidronate therapy for ~5 years before conception.

CASE PRESENTATIONS

Case 1

Mother: Mother 1 was a 19-year-old patient with OI type I (resulting from a nonsense mutation in the *COL1A1* gene) and sickle cell trait. Her first fracture was of a femur at 12 months of age. At 12 years of age, treatment with cyclical intravenous pamidronate was started because of recurrent lower limb and vertebral crush fractures. As described previously, pamidronate was given at a dose of 1 mg/kg on each of 3 consecutive days every 4 months.[1] This resulted in a total cumulative pamidronate dose of 49.5 mg/kg (9 mg/kg/year). Transiliac bone biopsy specimens performed at 8.3 and 15.4 years of age showed that pamidronate therapy was associated with a significant reduction in cancellous bone turnover, because bone formation rate per bone surface decreased from 100 (193% of age-matched mean for healthy children) to 6 $\mu m^3/\mu m^2$/year (17% of the age-matched mean value). At 17 years of age, she became pregnant with her first child, after which time no further pamidronate was given. The pregnancy was complicated by first trimester hyperemesis requiring intravenous rehydration. Throughout pregnancy, she received daily doses of 1000 mg elemental calcium and 400 IU of vitamin D. After 37 weeks of gestation, a male infant was born by spontaneous vaginal delivery. Mother 1 had serum calcium, phosphorus, alkaline phosphatase, and parathyroid hormone (PTH) concentrations within reference limits before pregnancy, as well as 24 h after the delivery and 11 days postpartum (Table 1).[12,13] Lumbar spine (L_1–L_4) areal BMD (aBMD) and antero-posterior height ratios of vertebral bodies at 11 days postpartum were similar compared with the last results before conception. At 8 months postpartum, she remained off pamidronate therapy, free of pain and fracture.

Baby: This child inherited his mother's *COL1A1* mutation and therefore has OI. He was born after 37 weeks of gestation with an Apgar score of 8 at 1 minute and 9 at 5 minutes. Birth weight was 3600 g (z score +0.5), and birth length was 50 cm (z score −0.2).[14] Blue sclera, but no dysmorphic features, fractures, or long bone deformities, was noted at birth. At 24 h of age, he had hypocalcemia with normal serum phosphorus and PTH concentrations (Table 1). He was asymptomatic at this time, as evident by normal feeding and lack of irritability, jitteriness, tremors, muscle twitching, or respiratory distress. There was no clinical evidence of a cardiac rhythm disturbance, although an electrocardiogram was not performed. He was discharged from hospital observation at 36 h of age and fed a standard infant formula. On day 11, his serum calcium was normal (Table 1).[12,13] A skeletal survey at this time was normal, with no evidence of fracture, abnormal bone development, or modeling defect (Fig. 1). There was no evidence of Wormian bones in the skull. aBMD on day 11 was within the limits for values observed in healthy babies (Table 1).[15] At 16 months of age, he remained free of fracture and had normal length (78.6 cm, z score −0.8) and weight (10.4 kg, z-score −0.6).[14]

Case 2

Mother: Mother 2 was a 19 year old with OI type IV caused by a glycine substitution in *COL1A1*. Her first fracture was of a tibia at 19 months of age. She had received cyclical intravenous pamidronate as described above from 12.5 to 17.8 years of age, with a cumulative pamidronate dose of 48 mg/kg (9 mg/kg/year). Histomorphometry of a transiliac bone specimen obtained at 16.4 years of age revealed that bone formation rate per bone surface had decreased from 63 $\mu m^3/\mu m^2$/year (183% of the age-matched mean) at the start of pamidronate treatment to 10 $\mu m^3/\mu m^2$/year (26% of age-matched mean). Conception occurred at 17.8 years of age, and no further pamidronate was given. The pregnancy was uneventful, and a live female infant was born through an elective lower segment caesarian

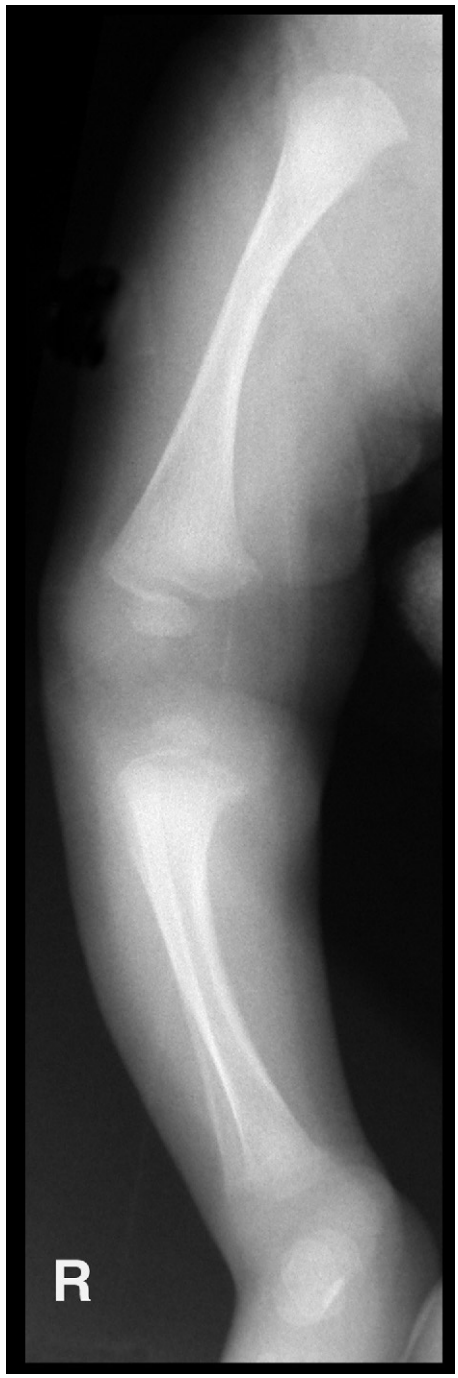

FIG. 1. Radiograph of the right lower extremity of the case 1 baby at 11 days of age. The bones are straight, appropriate in length, and have undergone normal development, showing no evidence of a modeling defect. The radiographs from the case 2 baby were similar.

section (for maternal pelvic deformity) at 38 weeks of gestation. Mother 2 received 1000 mg of elemental calcium and 400 IU of vitamin D per day throughout the pregnancy. Her serum calcium, phosphorus, alkaline phosphatase, and PTH concentrations were normal at the last pamidronate cycle before conception, as well as at 13 days postpartum (Table 1).[12,13] Postpartum lumbar spine aBMD and anteroposterior height ratios of lumbar vertebral bodies were similar to the last results before conception. At last follow-up (14 months postpartum), she remained off pamidronate therapy, free of pain and fractures.

Baby: The child of mother 2 inherited her *COL1A1* mutation and therefore has OI. She was born at 38 weeks of gestation with Apgar scores of 8 at 1 minute and 10 at 5 minutes. Birth weight was 2860 g (z score −0.7), and birth length was 48 cm (z score −0.8).[14] She was free of fracture at birth, but was noted to have bilateral talipes equinovarus. The limbs were otherwise straight. Calcium concentrations were not measured in the first few days of life, but there were no signs or symptoms suggesting hypocalcemia. Feeding was started using a standard infant formula, and baby 2 was discharged home on day 4 of life after an uneventful postnatal period. At 13 days of age, she was noted to have blue sclera. Her cardiovascular, respiratory, gastrointestinal, and neurological systems were normal on clinical examination. A skeletal survey showed Wormian bones on the skull radiograph, but was otherwise normal. Lumbar spine aBMD was within the reference range for age (Table 1).[15] Serum biochemical analysis was normal, although ionized calcium was not available (Table 1).[12,13] Her bilateral talipes equinovarus was treated with serial casting and percutaneous bilateral Achilles' tenotomies. At 14 months of age, she was well and free of fracture, with normal length (79.5 cm, z score +0.6) and weight (10.8 kg, z score +0.5).[14]

DISCUSSION

This is the first report on maternal and fetal outcomes after prolonged pamidronate therapy before conception. Both pregnancies were uneventful, apart from hyperemesis in mother 1. Labor was not prolonged, and there was no clinical evidence of hypocalcemia during parturition.

During the third trimester of pregnancy, fetal calcium requirements may outstrip maternal intestinal absorption, resulting in the resorption of calcium from the maternal skeleton.[16,17] Previous maternal pamidronate administration might therefore reduce the amount of skeletally derived calcium that is available for fetal bone mineral accrual. However, although both mothers had histomorphometric evidence of significantly reduced bone turnover, both babies in this report had normal BMC and aBMD at birth, suggesting that intrauterine calcium accretion had been normal.

During lactation, maternal calcium requirements are met through a PTH-related peptide mediated demineralization of the maternal skeleton.[17] While there are no human data, bovine studies have shown that bisphosphonate therapy during lactation can disrupt this process, resulting in severe maternal hypocalcemia.[18] At the present time, therefore, it seems advisable that women previously treated with bisphosphonates do not breast feed. Both mothers in this report bottle-fed their infants.

During pregnancy, women with OI experience a high incidence of back pain, possibly related to vertebral crush fractures.[19] The two women in this report experienced no back pain, vertebral shape did not change, and their aBMD remained stable throughout pregnancy. These findings may

represent a beneficial effect of prepregnancy pamidronate treatment. It is difficult to evaluate if the babies derived any benefit from exposure to pamidronate that was released from the mothers' skeleton. The clinical course of the babies was in keeping with that of their mothers and did not differ from that of other babies with types I and IV OI. Lumbar spine aBMD of the two babies fell within the range that we have observed in 11 other neonates with OI (median, 0.174 g/cm^2; range, 0.098–0.240 g/cm^2).

Neither infant had evidence of abnormal skeletal modeling. However, baby 2 was born with bilateral talipes equinovarus, a deformity that has an incidence between 0.93 and 6.8 per 1000 live births in the general population.[20] The incidence of talipes equinovarus in OI patients is unknown, but we have observed it in two (baby 2 and a baby with OI type I) of about 400 children with OI who were evaluated at our institution during the past 5 years (unpublished observations). While we cannot rule out an association between the development of this skeletal deformity and previous maternal pamidronate treatment, no animal model has shown similar skeletal deformities after antenatal bisphosphonate exposure.

Baby 1 had an ionized calcium concentration at 24 h of age below the published reference value, which may have resulted from an antiresorptive effect of pamidronate on the baby's skeleton. However, the ionized calcium concentration did not decrease below levels that are commonly seen at 24 h of age, a time when ionized calcium normally reaches its nadir,[21] and he remained asymptomatic without specific intervention. Nevertheless, it is certainly advisable to monitor calcium levels of neonates born to mothers who were previously treated with pamidronate and to evaluate for signs and symptoms of hypocalcemia.

In conclusion, these two cases do not provide evidence that maternal health during pregnancy is adversely affected by pamidronate treatment that is administered before conception. However, it cannot be excluded that the adverse events (hypocalcemia and talipes equinovarus) that were observed in the babies might be related to prior pamidronate treatment of the mother. Because bisphosphonates are increasingly used to treat adolescents and premenopausal women, it is clearly necessary to perform systematic studies on the outcome of pregnancy of women who for any reason have received bisphosphonate therapy before conception.

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