

CLINICAL CASE SEMINAR

Maternal and Infant Outcome after Pamidronate Treatment of Polyostotic Fibrous Dysplasia and Osteogenesis Imperfecta before Conception: A Report of Four Cases

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Background: Pamidronate is used extensively for treatment of osteoporotic and high bone turnover conditions. Because it has a long retention time in the human skeleton, concerns have been raised as to safety profile in women of child-bearing age.

Methods: Four infant outcomes of pregnancies of three women, two with polyostotic fibrous dysplasia and one with osteogenesis imperfecta, all of whom were treated with iv pamidronate before conception, are reported, with biochemical, radiological, and bone density data.

Results: Each pregnancy was uncomplicated, and the four offspring are healthy, with no evidence of biochemical or skeletal abnormality.

Conclusions: We found no evidence for adverse effects of prepregnancy pamidronate on maternal or fetal health. Until the results of systematic studies are available, caution is recommended regarding pamidronate use in women of child-bearing years. (*J Clin Endocrinol Metab* 91: 2017–2020, 2006)

McCUNE-ALBRIGHT SYNDROME is characterized by polyostotic fibrous dysplasia of bone, café au lait markings, precocious puberty, and other endocrinopathies. Osteogenesis imperfecta (OI), caused by mutations of the COL 1 A1 gene, also results in multiple fractures, pain, and increasing physical disability. Bisphosphonate treatment of both polyostotic fibrous dysplasia and OI has been reported to reduce pain and fracture rate of affected areas (1–4). Bisphosphonates are also known to persist in mineralized bone for many years and to cross the placenta in animals and humans. Concerns have been raised that, during pregnancy, the fetus may potentially be exposed to bisphosphonate release from maternal bone if the mother received bisphosphonates before conception and that reduced bone turnover may cause problems with maternal outcome (5). There has previously been only one report concerning safety issues published, of two women who received long-term iv pamidronate therapy before conception (6). In that report, one baby had transient asymptomatic hypocalcemia and one had bilateral talipes equinovarus in the neonatal period, but both the mothers and babies remained well and free of fracture up to 16 months postpartum.

Patients and Methods

All adult subjects in this case report gave informed consent for participation of themselves and their infants for the study.

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Abbreviations: BMD, Bone mineral density; DXA, dual-energy x-ray absorptiometry; OI, osteogenesis imperfecta.

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Data for pamidronate dosing schedules are shown in Table 1. Data for maternal and child biochemistry are summarized in Table 2.

Case 1

Mother 1 is a 39-yr-old woman diagnosed with McCune-Albright syndrome at age 27 yr, with polyostotic fibrous dysplasia, café au lait spots, and facial asymmetry secondary to sphenoid expansile lesions, but currently she has no other endocrinopathies. Menarche was at 12 yr. Bone pain in the pelvis, limbs, and skull was noted from 8.5 yr of age. Associated bony deformities of the femuri were treated surgically in her birth country. She had two healthy children before a late presentation for pain control. She commenced iv disodium pamidronate treatment at 28 yr [1 mg/kg for 3 d (3 mg/kg per dose) every 4–6 months], with 7.5 mg/kg-yr cumulative dose. Improvement of bone pain and mobility was reported.

Pamidronate therapy was ceased at age 32, after 4 yr of treatment, at the time the patient stated she was planning a pregnancy. She was advised to wait for at least 6–12 months before attempting a pregnancy, but conception occurred 3 months later. The pregnancy was uneventful apart from some back discomfort, with a normal vaginal delivery at 38 wk gestation of a healthy female infant (baby 1).

Intravenous pamidronate of 1 mg/kg, administered every second month, was restarted 18 months postpartum because of increasing leg pain caused by a stress fracture on the upper end of the left femur in an area of extensive fibrous dysplasia. Dosing schedule was changed to every third month once pain control was established. Dual-energy x-ray absorptiometry (DXA) monitoring of bone mineral density (BMD) was undertaken and was normal (Table 2).

Baby 1 was born at 38 wk gestation with a birth weight of 2.5 kg. She was clinically normal, with no obvious skeletal abnormalities. There was no report of any perinatal irritability or twitching. She was breastfed up to 18 months of age, before changing to bottle feed as her mother restarted pamidronate treatment. Motor milestones were normal. She walked at 10 months of age. Investigation of the child was refused until she was aged 4 yr, at which time she had a DXA scan, normal serum biochemistry (Table 2), and a normal long-bone x-ray (Fig. 1A). At that

TABLE 1. Pamidronate doses for patients

Subject	Age started pamidronate	Age completed pamidronate	Duration of treatment (months)	Dose schedule (mg/kg per dose)	Dose schedule (mg/kg-yr)	Last dose before conception (months)
1	28	32	46	3	7.5	3
2	25.8	28	26	3	9	3, baby 2; 48, baby 3
3	24.5	26	19	1	6	21

time, her height was on the 75th centile for age, in a family with a midparental height expectation on the 75th centile.

Cases 2 and 3

Mother 2 is a 35-yr-old woman who presented with shin pain secondary to fibrous dysplasia of the left lower limb at 20 yr of age. She had a history of untreated precocious puberty but no other features of the McCune-Albright syndrome. She began 1 mg/kg iv pamidronate infusions for 3 d (3 mg/kg per dose) every 4–6 months at age 25.8 yr, with a cumulative dose of 9 mg/kg-yr, for continued bone pain in the left femur and reported marked improvement in pain control and mobility.

She became pregnant unexpectedly for the first time at age 28 yr, after 2.2 yr of treatment. Her last pamidronate infusion was 3 months before conception. After an uneventful pregnancy and labor, she delivered a full-term healthy boy (baby 2). She did not recommence pamidronate and did not attend for medical review. A second uneventful pregnancy occurred at age 31 yr, with the full-term vaginal delivery of a healthy boy (baby 3).

Mother 2 has not received any additional bisphosphonate therapy and remains relatively pain free and normally mobile, with no fractures reported.

Babies 2 and 3 were both healthy at birth, with no neonatal complications and no obvious skeletal deformities. Both children were breastfed. Motor milestones were normal. Serum biochemistry, which was normal, and DXA scans were performed at 4 yr (baby 1) and 8 months (baby 2) of age, respectively (Table 2). Long-bone x-rays are shown in Fig. 1, B and C. Both children remain fracture free and asymptomatic. Both are on the 95th centile in a family in which the midparental height expectation is on the 60th centile and continue to grow at a normal rate.

Case 4

Mother 3 is a 28-yr-old woman, diagnosed with OI type IV at age 2 yr, with a history of multiple low-impact or nontraumatic fractures and with blue sclerae. Treatment with 1 mg/kg pamidronate per dose, every 2 months, with a cumulative dose of 6 mg/kg-yr, was given between the

ages of 24 and 26 yr, with significant improvement in clinical pain, physical activity, and bone mineral density. She elected to cease treatment in 2003 in preparation for conception, which occurred 21 months later. The pregnancy was complicated by severe back and pelvic pain, necessitating early delivery at 34 wk gestation. Baby 4 was breastfed for 6 wk only.

Mother 3 has requested recommencement of pamidronate treatment 2 months postpartum for pain control and also with the aim of interim bone protection before considering another pregnancy. Normal DXA scans and biochemistry are shown in Table 2.

Baby 4 was born at 34 wk gestation, weighing 2270 g. The perinatal course was uneventful. She remains well, with normal motor milestones at 2 months. She has no signs of OI so far. Sclerae are not blue, and no fractures have occurred. At 51 cm, she is on the 50th centile in length for age corrected for gestation. DXA scan and normal serum biochemistry are shown in Table 2. Long-bone x-ray is seen in Fig. 1D.

Discussion

This is the second report of maternal and fetal outcomes after prolonged pamidronate therapy before conception. The four pregnancies and labors reported were similarly uneventful, apart from back pain reported by mothers 1 and 3 in the third trimester.

Pamidronate is known to persist in mineralized bone for many years (5). Thus, it has been suggested that prepregnancy administration of pamidronate may alter fetal bone modeling and reduce the amount of resorbable bone calcium available to the fetus during the third trimester (7, 8). High-dose bisphosphonate therapy during rat pregnancies has been shown to result in shortening of diaphyseal bone, increased diaphyseal trabecular volume, and a reduction in bone-marrow volume in the fetus (8, 9) and is contraindicated during a pregnancy due to possible bone toxicity. A

TABLE 2. Clinical, biochemical, and bone density parameters for mothers and infants

	Height (cm) [centile]	Time of study	Calcium (2.10–2.60 mmol/liter)	Phosphate, aged 2 yr to adult (1.10–1.80 mmol/liter); aged 2 wk to 2 yr (1.3–2.0 mmol/liter)	PTH (0.5–5.9 pmol/liter)	ALP adult (100–300 IU/liter); child (100–350 IU/liter)	Vitamin D (>50 nmol/ liter)	BMD (g/cm ²): a, lumbar; b, NOF	z score: a, lumbar; b, NOF
Mother 1	158.4 [25th]	Preconception	2.31	0.96	ND	226	ND	a, 0.983 b, 0.985	a, –1.0 b, +0.09
Mother 1	158.4	5 yr postpartum	2.38	0.98	1.4	177	79	a, 1.075 b, 0.931	a, +0.21 b, –0.69
Child 1	108.6 [75th]	Aged 4 yr	2.48	1.51	ND	281	ND	a, 0.544 b, 0.463	b, –1.1
Mother 2	167.0	Postconception, baby 3	2.40	0.82	3.7	73	55.9	a, 1.167 b, 0.908	a, 1.1 b, 0.1
Child 2	111.0 [95th]	Aged 4 yr	2.39	1.49	1.2	231	72	a, 0.530 b, 0.473	0.8
Child 3	68 [95th]	Aged 8 months	2.52	1.92	1.1	181	77	a, 0.384 b, 0.283	N/A
Mother 3	147.0	Postpartum	2.41	1.45	3.2	77	75	a, 0.698 b, 0.738	a, –3.2 b, –2.9
Child 4	51 [50th]	8 wk	2.70	2.15	1.0	164	101	b, 0.127	N/A

ALP, Alkaline phosphatase; NOF, neck of femur; ND, not performed; N/A, not available because no standards for age. Conversion from metric to international units: calcium, total, serum mmol/liter \times 4 = mg/dl; phosphorus, serum mmol/liter \times 3.096 = mg/dl. There is no accepted conversion for the alkaline phosphatase method (Vitros 950 analyzer supplied by Ortho Clinical Diagnostics, Raritan, NJ); PTH, intact, serum pmol/liter \times 9.497 = pg/ml; 25OH vitamin D₃, serum nmol/liter \times 0.40 = ng/ml. BMD database derived from the data of the manufacturer for Hologic (Bedford, MA) QDR 4500, University of Illinois (Chicago, IL) (13).

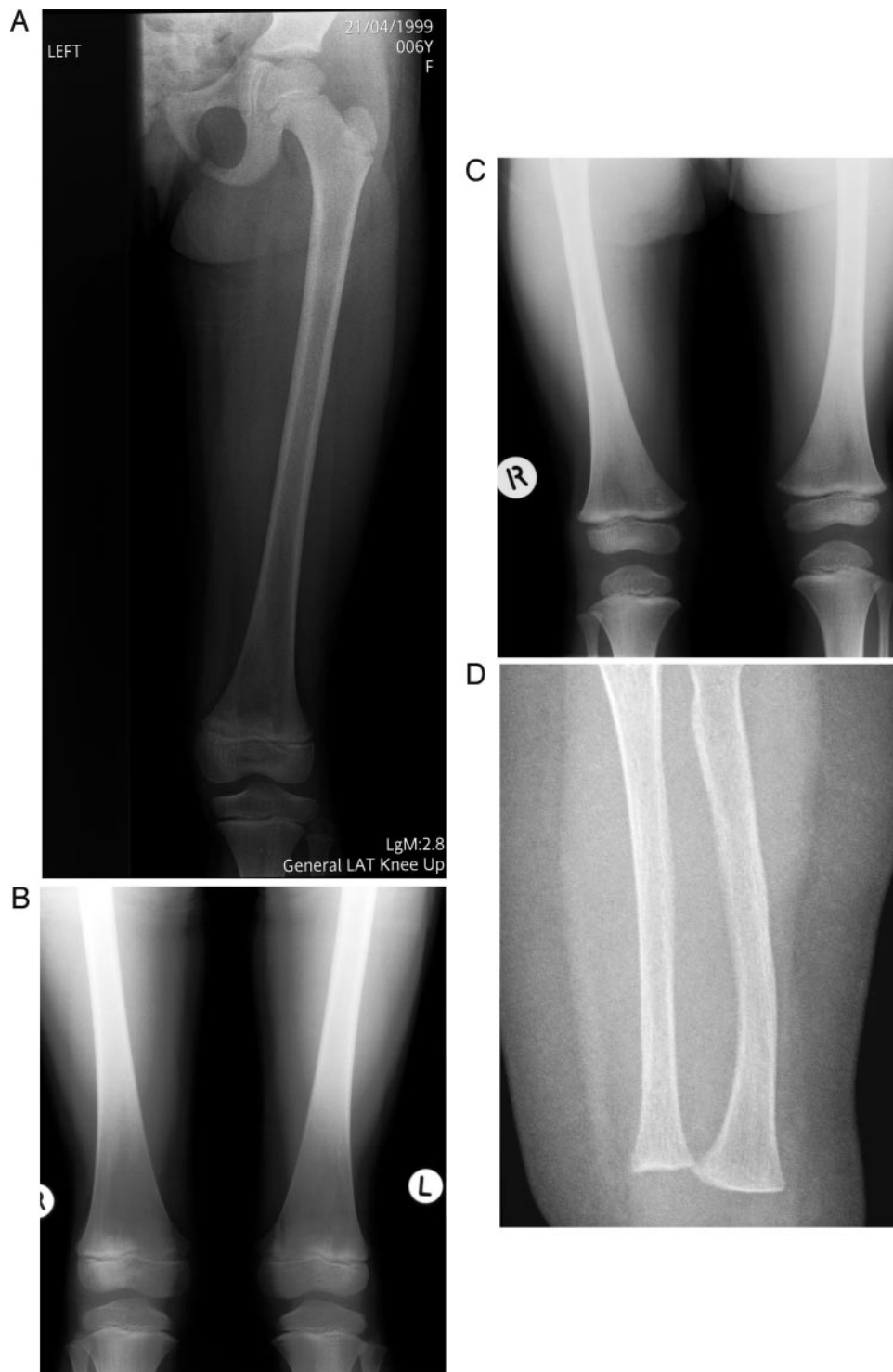


FIG. 1. Long-bone x-ray for children 1–3. A, Child 1. B, Child 2. C, Child 3. D, Baby 4.

case report of pamidronate given during pregnancy for metastatic cancer (10) did not demonstrate adverse outcome to mother or infant.

The theoretical risk to the fetus of bony toxicity or modeling abnormality attributable to leaching of pamidronate from the maternal skeleton has so far not been shown in

humans. There is a large variation in reported retention rate of bisphosphonate in the skeleton after administration, which does not change with subsequent doses (9). This suggests, but does not prove, a very low possible blood level reaching the fetus.

Animal studies suggest that bisphosphonates can disrupt

maternal calcium metabolism with severe hypocalcemia during lactation by reducing the amount of releasable skeletal calcium availability (11), and that a similar effect may be seen in humans. Mothers 1 and 2 in this report breastfed for 15–18 months and remained clinically eucalcemic during this period without vitamin D supplementation. More studies are required to define this risk. No evidence for pamidronate excretion has been reported in one case (12).

In conclusion, these three cases support the previous two reported and do not provide any evidence that maternal health during pregnancy is adversely affected by pamidronate treatment before conception. The four pediatric cases also do not provide any evidence of adverse fetal effects of prepregnancy pamidronate. However, more systematic studies are still necessary on the outcome of pregnancy of women who have been treated with iv bisphosphonates before conception, and caution needs to be expressed as to safety until results of such studies are available.

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