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Research Letter

Uncomplicated vaginal delivery in two consecutive pregnancies carried to term in a woman with osteogenesis imperfecta type I and bisphosphonate treatment before conception

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A 26-year-old, primigravid woman was referred for genetic counseling at 16 weeks of gestation because of maternal osteogenesis imperfecta (OI) type I. She was 158 cm tall and had a body weight of 51 kg. She had blue sclerae and was known to have a mild form of OI type I; her father and sister were also affected. She had sustained fractures of distal phalanx of the left thumb and left radius. At 23 years of age, cyclical intravenous bisphosphonate (pamidronate) had been started because of recurrent fractures and bone pain. The treatment with pamidronate was given at a dose of 15 mg/month. Pamidronate therapy was ceased 1 month before the pregnancy. Prenatal ultrasound was unremarkable, and the fetal long bones were normal. The woman underwent amniocentesis at 16 weeks of gestation, and cytogenetic analysis revealed a karyotype of 46,XY. Level II ultrasound follow-ups in the third trimester showed a normal fetus with no bony abnormalities. At 37 weeks of gestation, she delivered a 2840-g boy uneventfully via the vaginal route. The baby was 53 cm tall and had blue sclerae, but was morphologically normal with no fractures. Neither the mother nor her son had hypocalcemia postpartum.

At the age of 4 years, the son suffered a fracture of the right humerus. He started intravenous pamidronate therapy at the age of 8 years. Molecular analysis revealed that both the mother and her son had a heterozygous deletion mutation of c.1380delT in exon 21 of the *COL1A1* gene resulting in a functional null allele (Fig. 1). The mutation caused a frameshift (p.G461AfsX79), introducing 78 novel residues at codon 461 and resulting in a premature termination codon that removed all the following amino acids of the protein. Six months after delivery, the woman's bone mineral density of lumbar spine (L2-L4) was checked and found to be 0.847 g/cm^2 (−2.59 SD from T-score), and she started intravenous pamidronate therapy at 30 mg/month. Eighteen months after the first pregnancy, the woman ceased pamidronate therapy and started oral bisphosphonate therapy with alendronate 70 mg/week until 4 months before her second pregnancy at the age of 30 years. During the second pregnancy, prenatal ultrasound was normal, and she did not undergo any invasive prenatal diagnosis. At 38 weeks of gestation, she delivered a 3838-g healthy boy uneventfully via the vaginal route. The baby was normal and was not affected with OI. Both the mother and the normal son remained well 5 years postpartum.

The present case provides evidence for no adverse maternal and fetal outcome after long-term bisphosphonate treatment before conception in maternal OI type I. Bisphosphonates inhibit osteoclast activity and suppress bone resorption by

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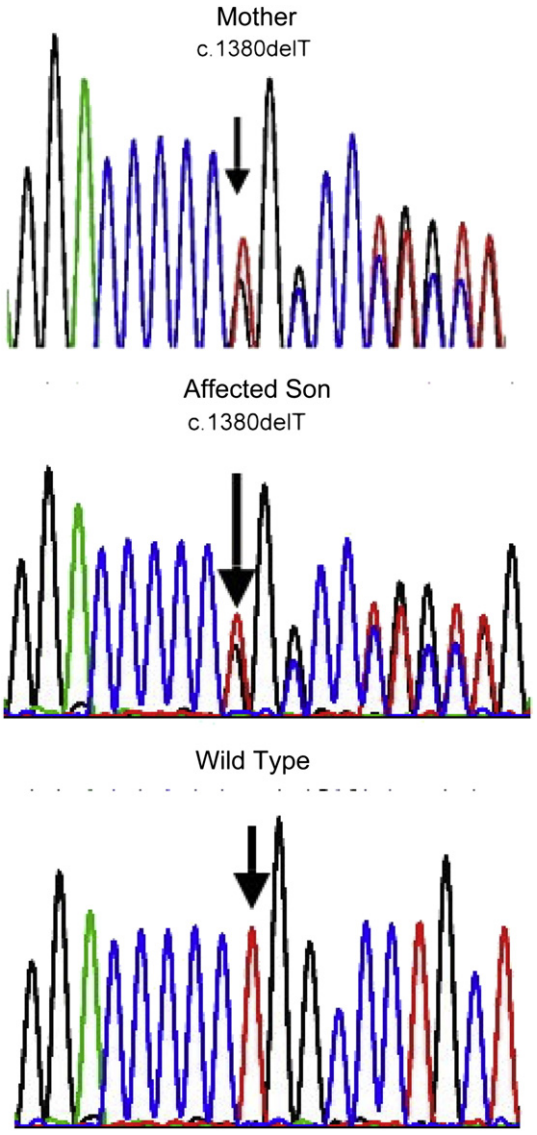

Fig. 1. Molecular analysis of the mother and her affected son shows that both individuals have a heterozygous deletion of c.1380delT in exon 21 in the *COL1A1* gene resulting in a functional null allele.

interfering with the mevalonate pathway of cholesterol biosynthesis [1−3]. Bisphosphonates have been used in preventing bone loss in the disorders of glucocorticoid-associated osteoporosis, OI and hypercalcemia associated with malignancy. The safety of bisphosphonates in women of child-bearing age raises concerns that the fetus may potentially be exposed to bisphosphonates released from the maternal bone if the mother received bisphosphonates before conception, or directly transmitted from the placenta if the mother receives bisphosphonates during pregnancy [4−6]. Therefore, it has been advised that all bisphosphonates are relatively contraindicated in females of reproductive age [7]. However, recent studies have shown that preconceptional and first-trimester use of bisphosphonates may not pose substantial fetal risks [8−11]. Munns et al. [8] first reported no adverse maternal and fetal outcome in two women with OI type I and IV who received long-term pamidronate treatment before conception. Chan and Zacharin et al. [9] found no evidence for adverse effects of pre-pregnancy pamidronate on maternal and fetal health in three women with polyostotic fibrous dysplasia and in one woman with OI type IV. Djokanovic et al. [10] reviewed 51 published cases of women exposed to bisphosphonates before or during pregnancy and found that none gave birth to infants with skeletal abnormalities or other congenital malformations. Levy et al. [11] followed 21 women exposed to bisphosphonates for 3 months or less before pregnancy in comparison with 21 matched controls and found no fetal risks in the preconceptional and first-trimester use of bisphosphonates. Our observation adds to the list of uncomplicated pregnancy outcome following *in utero* exposure to bisphosphonates.

The present case also provides evidence for uncomplicated pregnancy outcome of vaginal delivery for affected mothers and fetuses with non-lethal types of OI. In a study of 167 pregnancies with fetuses affected by OI, Cubert et al. [12] found that cesarean delivery did not decrease the fracture rate at birth in the infants with nonlethal forms and did not prolong survival for the infants with lethal forms and suggested that cesarean delivery should be reserved for standard obstetric indications in pregnancy with fetal OI. In cases of maternal OI with mild clinical features, vaginal delivery can be achieved. In a review of 15 pregnancies with maternal OI, Key and Horger [13] found that 60% (9/15) were delivered vaginally, and 40% (6/15) were delivered abdominally because of cephalopelvic disproportion, twins, a fragile fetus and previously fractured or deformed pelvis. Although vaginal delivery in maternal OI type I is relatively safe, careful obstetric surveillance is needed, and attention should be paid to uterine rupture because of the decreased amount of collagen in myometrium, postpartum hemorrhage as a result of uterine atony, lacerations and impaired platelet aggregation, and neonatal fracture associated with OI [13−19].

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References

[1] Fleisch H. Bisphosphonates: mechanisms of action. Endocr Rev 1998;19:80−100.
[2] Fisher JE, Rogers MJ, Halasy JM, Luckman SP, Hughes DE, Masarachia PJ, et al. Alendronate mechanism of action: geranylgeraniol, an intermediate in the mevalonate pathway, prevents inhibition of osteoclast formation, bone resorption, and kinase activation *in vitro*. Proc Natl Acad Sci USA 1999;96:133−8.
[3] Halasy-Nagy JM, Rodan GA, Reszka AA. Inhibition of bone resorption by alendronate and risedronate does not require osteoclast apoptosis. Bone 2001;29:553−9.
[4] Graepel P, Bentley P, Fritz H, Miyamoto M, Slater SR. Reproduction toxicity studies with pamidronate. Arzneimittelforschung 1992;42:654−67.
[5] Khan SA, Kanis JA, Vasikaran S, Kline WF, Matuszewski BK, McCloskey EV, et al. Elimination and biochemical responses to intravenous alendronate in postmenopausal osteoporosis. J Bone Miner Res 1997;12:1700−7.

[6] Marini JC. Do bisphosphonates make children's bones better or brittle? N Engl J Med 2003;349:423–6.
[7] McKenna M, Mansfield JC. Safety of bisphosphonates in women of child bearing age. Aliment Pharmacol Ther 2009;29:1214–5.
[8] Munns CFJ, Rauch F, Ward L, Glorieux FH. Maternal and fetal outcome after long-term pamidronate treatment before conception: a report of two cases. J Bone Miner Res 2004;19:1742–5.
[9] Chan B, Zacharin M. Maternal and infant outcome after pamidronate treatment of polyostotic fibrous dysplasia and osteogenesis imperfecta before conception: a report of four cases. J Clin Endocrinol Metab 2006; 91:2017–20.
[10] Djokanovic N, Klieger-Grossmann C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? J Obstet Gynaecol Can 2008;30:1146–8.
[11] Levy S, Fayez I, Taguchi N, Han J-Y, Aiello J, Matsui D, et al. Pregnancy outcome following *in utero* exposure to bisphosphonates. Bone 2009;44: 428–30.
[12] Cubert R, Cheng EY, Mack S, Pepin MG, Byers PH. Osteogenesis imperfecta: mode of delivery and neonatal outcome. Obstet Gynecol 2001;97:66–9.
[13] Key TC, Horger 3rd EO. Osteogenesis imperfecta as a complication of pregnancy. Obstet Gynecol 1978;51:67–71.
[14] Carlson JW, Harlass FE. Management of osteogenesis imperfecta in pregnancy. A case report. J Reprod Med 1993;38:228–32.
[15] Sharma A, George L, Erskin K. Osteogenesis imperfecta in pregnancy: two case reports and review of literature. Obstet Gynecol Surv 2001;56: 563–6.
[16] Krishnamoorthy U, Vausse S, Donnai P. Management of pregnancy complicated by maternal osteogenesis imperfecta. Report of a case with uterine rupture. J Obstet Gynaecol 2002;22:316.
[17] Di Lieto A, Pollio F, De Falco M, Iannotti F, Mascolo M, Somma P, et al. Collagen content and growth factor immunoexpression in uterine lower segment of type IA osteogenesis imperfecta: relationship with recurrent uterine rupture in pregnancy. Am J Obstet Gynecol 2003;189:594–600.
[18] Christodoulou S, Freemont AJ, McVey R, Vause S. Prospective comparative case study of uterine collagen in a woman with osteogenesis imperfecta type 1 who had previously ruptured her uterus. J Obstet Gynaecol 2007;27:738–9.
[19] Litos M, Michala S, Brown R. Osteogenesis imperfecta and pregnancy. Eur J Obstet Gynecol Reprod Biol 2008;136:126–7.