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LETTER

Maternal and fetal outcome after long-term bisphosphonate exposure before conception

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Dear Editors,

Despite a substantial increase in the use of bisphosphonates at childbearing age, very little is known regarding their risk during pregnancy. Bisphosphonate and particularly pamidronate therapy administered to girls and young women might adversely affect the outcome of subsequent pregnancies given the fact that bisphosphonates have been shown to cross the placenta in both animals and humans [1, 2] and persist in mineralized bone for many years [3]. In some published cases, bisphosphonate administration during human pregnancy was used to treat malignant hypercalcemia or pregnancy-associated osteoporosis without any adverse effects on the neonate [4, 5]. In 24 pregnancies following pre-pregnancy or early pregnancy alendronate treatment, it seems that alendronate does not have a major teratogenic risk [6]. There have previously been only two reports concerning pamidronate safety profile in women of childbearing age [7, 8]. In the first report, two women with osteogenesis imperfecta (OI) who received intravenous pamidronate before conception had an uneventful pregnancy. One baby had transient asymptomatic hypocalcemia and one had bilateral talipes equinovarus. In the second report, there were four pregnancies of three women, two with polyostotic fibrous dysplasia and one with OI. Each pregnancy was uncomplicated, and the four offsprings were healthy, with no evidence of biochemical or skeletal abnormalities. We report the outcome of a new pregnancy of a 30-year-old woman with a 1-year history of diabetes mellitus and OI type I, who received bisphosphonates (consecutively 10 mg oral daily alendronate for 6 months and 90 mg intravenous pamidronate every 4 months during 1 year) before conception. A normal pregnancy outcome was documented with a normal vaginal delivery at 39 weeks' gestation of a healthy female infant. The baby who weighed 4 kg did not present any malformation or perinatal irritability due to hypocalcemia or hypoglycemia. She was breastfed until she was 3 months old. At 2 months, an investigation of the child showed asymptomatic hypocalcemia (2.10 mmol/l, below the normal range (2.25–2.65)). At 5 months of age, normal calcemia and normal long-bone X-ray was documented. For the mother, we observed hypocalcemia (serum calcium level 2.11 mmol/l) at 8 weeks of gestation and at 3 months after delivery, but phosphorus and alkaline phosphatase were normal. At 6 months post partum, she remained free of pain and fracture. Lumbar spine BMD was similar compared with the last results before conception. She had not lost bone mass from the pregnancy and breast feeding.

Coupled with existing data in the literature (Table 1), our case shows that preconceptional bisphophonate therapy, and particularly pamidronate treatment, does not induce substantial fetal or maternal risks or serious adverse effects. Nevertheless, the harm of these agents remains unclear. Caution is mandatory until further information is available and bisphosphonate must be contraindicated in pregnancy. Risk and benefits of bisphosphonate should be carefully weighed in women at childbearing age. Further studies,

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Table 1 Cases of i.v. pamidronate treatment before conception in literature

Treatment indication, reference	Pamidronate treatment (duration; conception delay; cumulative dose)	Maternal outcome	Fetal outcome	Follow-up
OI type I [7]	5 yr; –; 9 mg/kg.yr	First trimester hypermesis	Full term; 3,600 g; male; asymptomatic hypocalcemia	16 mo
OI type IV [7]	5 yr; –; 9 mg/kg.yr	Uneventful pregnancy	Full term; 2,860 g; female; bilateral talipes equinovarus	14 mo
Polyostotic fibrous dysplasia [8]	4 yr; 3 mo; 7.5 mg/kg.yr	Back discomfort	Full term; 2,500 g; healthy female	4 yr
Fibrous dysplasia [8]	2.2 yr; 3 mo; 9 mg/kg.yr	Uneventful pregnancy	Full term; healthy boy	4 yr
Fibrous dysplasia [8]	2.2 yr; 48 mo; 9 mg/kg.yr	Uneventful pregnancy	Full term; healthy boy	8 mo
OI type IV [8]	2 yr; 21 mo; 6 mg/kg.yr	Severe back and pelvic pain	Prematurity; 2,270 g; female	2 mo
OI type I [our case]	1 yr; 2 mo; 4.6 mg/kg.yr	Uneventful pregnancy, well controlled diabetes	Full term; 4,000 g; healthy female	7 mo

OI osteogenesis imperfecta, *yr* year, *mo* months

reporting similar cases, are useful to identify risks of bisphosphonate on human pregnancy.

Conflicts of interest None.

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