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SHORT COMMUNICATION

Pregnancy-associated spinal osteoporosis treated with bisphosphonates: long-term follow-up of maternal and infants outcome

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Abstract Pregnancy-associated spinal osteoporosis (PPSO) is a rare condition characterized by severe back pain occurring near the end of the first pregnancy or shortly afterward. The aim of this report is to present a 12-year follow-up of a patient with PPSO. Also, the outcomes of patient's two pregnancies and her infants after long-term treatment with bisphosphonates are assessed. A young woman was referred to our tertiary care hospital aged 30 years, due to intense pain in thoracic and lumbar region that started during the last month of her first pregnancy and got worse after delivery. Bone mineral density (BMD) measurement, clinical, and biochemical parameters were performed. Extremely low lumbar spine BMD, L2–L4: 0.627 g/cm^2, T-score −4.8, Z-score −4.3, 52% young adult indicated severe osteoporosis. Cyclical treatment with etidronate and then pamidronate was started, and a substantial increase in the BMD and the reduction in back pain intensity were observed. An increase in BMD of 44.8% over baseline was observed after 12 years of follow-up. Her two pregnancies were uneventful, and no neonatal adverse effects were observed. Control DXA scan in her girl child aged 6.8 years revealed low BMD at the lumbar spine. As PPSO seems to be an underdiagnosed severe disease, caution is recommended if back pain occurs in the last trimester or early post-partum period. Although pre-pregnancy use of bisphosponates does not pose a substantial fetal risk, their use in women of childbearing age might best be done only when strong clinical indications exist.

Keywords Osteoporosis · Pregnancy · Lumbar spine · Bone mineral density · Bisphosphonates

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Introduction

The main forms of pregnancy-related osteoporosis are post-pregnancy spinal osteoporosis (PPSO), transient osteoporosis of the hip, and osteoporosis associated with heparin. Pregnancy-associated spinal osteoporosis (PPSO) is an uncommon condition which etiology and natural history are largely unknown. PPSO is a potentially devastating disorder that is characterized by back pain near the end of the first pregnancy or post-partum period in affected women. Loss of height due to vertebral compression and vertebral fractures could be associated with this form of osteoporosis [1–3]. The optimal management of this condition is not established, and the data on the use of antiresorptive therapy with bisphosphonates (BP) and long-term outcomes are limited. BP are stable analogs of pyrophosphate that inhibit osteoclast-mediated bone resorption, but could also interfere with normal bone and cartilage mineralization [4]. BP are used for the treatment of osteoporosis, Paget's disease, bone metastases, osteogenesis imperfecta, and other conditions characterized with excessive bone resorption. The increased use of BP in women of childbearing age raises concerns about their

teratogenic effects. BP are rapidly cleared from the blood, but the proportion (average 68%, range 12–98%) remains deposited in the bone matrix for years in pharmacologically inactive form [5]. As BP released back in the circulation can cross the human placenta, care should be taken when BP are used before or during the pregnancy. Their long-term effects on the fetal skeletal growth and development are not known [6].

In this article, we report a case of a young woman with pregnancy-associated spinal osteoporosis who received long-term bisphosphonate treatment before conception of her second and third child. Maternal and infant outcomes are assessed during a 12-year follow-up.

Clinical report

We present a case of a 42-year-old woman who was initially referred to our Outpatient Clinic 3.5 months after delivering her first child at the age of 30 years. She presented with complaints of severe pain in thoracic and lumbar spine region that caused marked difficulties in daily activities. Intense back pain started during the last month of her first pregnancy and gotten worse after delivery. Prior to the referral to our clinic, she was diagnosed with low back pain syndrome in other medical center and received treatment with physical modalities and NSAIDs without beneficial effects. The patient's menarche occurred at 13 years of age and her menses had been regular since the menarche. There was no history of trauma, menstrual irregularities, or underlying diseases. She had no history of fractures and had not taken drugs that could reversely affect the bones. There were no signs of metabolic, infectious, or malignant bone diseases. She was a non-regular, mild smoker for 4 years and had no other risk factors or positive family history for osteoporosis. A nutritional questionnaire showed that her daily calcium intake was about 1,000 mg and she was regularly exposed to sunlight. She was not taking calcium or vitamin D supplements during the pregnancy.

Physical examination

On physical examination, marked tenderness in thoracic vertebrae with deformation in the form of thoracic kyphosis posture was revealed. Her height was 152 cm and weight 52 kg, body mass index (BMI) 22.5.

Radiological examination

On thoracolumbar spinal radiographs, the increase in transparency of vertebral bodies was found. No vertebral compression or fractures were observed.

Bone mineral density

We measured lumbar spine bone mineral density using a dual-energy X-ray absorptiometry (Lunar DPX-L). Lumbar spine BMD was extremely decreased: L2–L4: 0.627 g/cm^2, T-score −4.8, Z-score −4.3, 52% young adult. The diagnosis of post-pregnancy spinal osteoporosis was established.

Biochemical evaluation

The laboratory assessments including erythrocytes sedimentation rate (ESR), serum and 24-h urine calcium (Ca) and phosphorus (P), creatinine (Cr), liver enzymes (AST, ALT), alkaline phosphates (ALP), thyroid hormone (TSH), and para-thyroid hormone (PTH) revealed no abnormality.

She was advised to stop breastfeeding. The therapy with elementary calcium (500 mg/day), vitamin D3 (400 IU/day), and calcitonin (100 mg/day i.m. for 7 days followed by 300 mg/week for 3 weeks) started immediately followed by cyclic intermittent therapy with etidronate (400 mg/day for 14 days every 3 months). Informed consent discussion was conducted with the patient in relation to etidronate treatment which was the only bisphosphonate drug available in our country at that time point.

She responded well to treatment with bisphosphonates. Her back pain gradually decreased over the next several months. At a 6-month follow-up, DXA scan revealed that BMD at the lumbar spine (L2–L4: 0.713 g/cm^2, T-score −4.1, Z-score −3.6) has increased for 13.7% over baseline. After 1-year therapy with etidronate, BMD at the lumbar spine (L2–L4: 0.814 g/cm^2, T-score −3.2, Z-score −2.7) showed an increase of 29.8% over baseline (Fig. 1). After 1.5 years, the therapy with etidronate was discontinued and she got pregnant. She was asymptomatic during her second pregnancy. One month after delivery, her BMD at the lumbar spine (L2–L4: 0.863 g/cm^2, T-score −2.8, Z-score −2.5) showed an increase of 37.6% compared to the pre-treatment values. She continued cyclical therapy with etidronate for another 2 years, after which she got pregnant for the third time. The therapy with bisphosphonates was discontinued 3 months before conception. She was symptom-free during her third pregnancy, and 2.5 months after delivery, her BMD at the lumbar spine (L2–L4: 0.810 g/cm^2, T-score −3.3, Z-score −3.3) revealed a decrease of 6.1% compared to the previous measurement. She continued antiresorptive therapy with pamidronate (30 mg, IV infusion every 3 months) for another 2 years after which DXA scan revealed BMD at the lumbar spine L2–L4: 0.908 g/cm^2, T-score −2.4, Z-score −2.4. An increase in BMD of 44.8% over baseline was observed.

At the control visit at the age of 42 years and 3 years after discontinuation of bisphosphonate therapy, BMD at

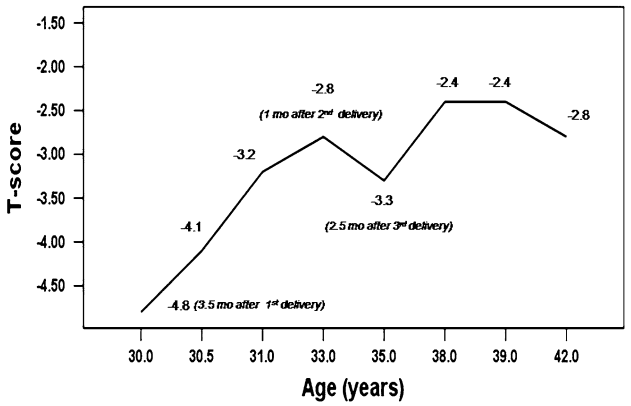

Fig. 1 BMD of lumbar spine in mother with PPSO who were followed for 12 years

the lumbar spine (L2–L4: 0.859 g/cm^2, T-score −2.8, Z-score −2.5) showed an increase of 37% over the basal values. At present, she is on therapy with calcium and vitamin D supplements.

First baby

After an uneventful pregnancy and labor, she delivered a full-term healthy boy (baby 1). The first infant lumbar spine DXA scan (LUNAR Prodigy Advance) was done at the age of 8.8 years: BMD L1–L4: 0.690 g/cm^{2,} Z-score −0.2. Control DXA scan was done at the age of 12.1 years and revealed BMD L1–L4: 0.784 g/cm^{2,} Z-score −0.2 (Table 1).

Second baby

She became pregnant for the second time at the age of 33 years, after she has been on bisphosphonate treatment for 1.5 years. Her last cycle of etidronate was 3 months before conception. Her second pregnancy and labor were uneventful and she delivered a full-term boy (baby 2). The baby was healthy at birth, with no neonatal complications, no obvious skeletal deformities or hypocalcaemia. The child continues to grow at a normal rate. DXA scan done at the age of 5.6 years revealed BMD L1–L4: 0.541 g/cm^{2,} Z-score −1.1. Control DXA scan was done at the age of 8.9 years and showed BMD L1–L4: 0.686 g/cm^2, Z-score −0.3 (Table 1).

Third baby

At the age of 35 years she got pregnant for the third time. She has been on bisphosphonate treatment for 3.5 years before conception. She received her last cycle of etidronate 3 months before conception. After a normal pregnancy and labor, she delivered a full-term girl (baby 3). The baby was healthy at birth and with no neonatal complications, no obvious skeletal deformities or hypocalcaemia. The child continues to grow at a normal rate. DXA scan done at the age 6.8 years revealed low lumbar spine BMD, BMD L1–L4: 0.538 g/cm^{2,} Z-score −1.6 as shown in Table 1.

Discussion

Pregnancy-related osteoporosis is a rare condition and its cause and pathophysiology remain unknown. The majority of cases of pregnancy-associated spinal osteoporosis are reported in primagravid women. The natural course and therapeutical management are poorly defined. PPSO is characterized by the presence of back pain and in some cases vertebral fractures and height loss could occur. It is not clear whether this condition is a consequence of pregnancy or pre-conception condition of low peak bone mass [7]. Low dietary calcium intake and vitamin D insufficiency in pregnancy can contribute to an excessively increased bone turnover. The high calcium demand during pregnancy and lactation may lead to its desorption from maternal skeleton leading to a reversible reduction in lumbar spine BMD of 5% [8] or 3–9% [9, 10], according to the reports. In a study of 13 cases with pregnancy- and

Table 1 Bone mineral density in infants

Infants	Pre–pregnancy etidronate treatment	B. height (cm)/B. weight (kg); BMI[a]	DXA scan (age, years)	Lumbar spine BMD (g/cm^2)	Z-score				
					L1–L4	L1	L2	L3	L4
First baby	None	139/31; 16.04	8.8	0.690	−0.2	−0.1	−0.5	−0.4	0.0
		161/44; 16.97	12.1	0.784	−0.2	−0.2	−0.4	−0.2	−0.1
Second baby	1.5 years	115/21; 15.88	5.6	0.541	−1.1	−1.0	−1.7	−0.8	−1.0
		138/30; 15.75	8.9	0.686	−0.3	−0.2	−0.5	−0.2	−0.3
Third baby	3.5 years	129/24; 14.42	6.8	0.538	−1.6	−1.1	−1.4	−1.2	−2.5

[a] Body mass index (BMI) was plotted according to BMI-children charts

lactation-associated osteoporosis by Phillips et al. [11], the significantly decreased lumbar spine BMD values have not returned to normal values after pregnancy. Currently, the development of PPSO cannot be predicted.

The data regarding the optimal therapy for PPSO, especially the use of bisphosphonates, are limited. The use of bisphosphonates in women of reproductive age raises concerns about its teratogenic effects. Whether the weaning and calcium and vitamin D supplements are sufficient to achieve recovery of bone loss is under discussion. Bisphosphonates have been used as antiresorptive drugs in some cases [12], and also the use of strontium ranelate [13] and teriparatide [14] have been described. Some of the most severe cases required kyphoplasty [15].

The most appropriate management of PPSO remains uncertain. It remains to be clarified whether the use of bisphosphonates is optimal treatment of PPSO. In the presented case, the significantly decreased BMD below the threshold of osteoporosis accompanied with severe back pain justified the use of bisphosphonates for prevention of vertebral fractures. The intermittent cyclical etidronate therapy was well tolerated and effective. At a12-year follow-up, our patient had a 37% increase in lumbar spine BMD over a baseline. Teratogenic effects of bisphosphonates are not known. Care should be taken when prescribing BP in women of childbearing age as these compounds can cross the human placenta and interfere with fetal bone metabolism [6]. Animal studies have shown that very large doses of etidronate, hundred times exceeding maximal dose for humans, administered during pregnancy caused fetal skeletal malformations [16]. In this report, there was no evidence of adverse effects in two infants after long-term maternal pre-pregnancy use of bisphosphonates. A recent study in 21 women has assessed the pre-pregnancy or in the first 3 months of pregnancy use of several bisphosphonates (alendronate, etidronate, risedronate, and pamidronate) and concluded that bisphosphonates do not have substantial fetal risk with and no neonatal adverse effects [17]. Several studies have also proved that the therapy with aminobisphosphonates have not affected the fetal bone modeling and development [18–20].

It is not clear whether the low lumbar spine BMD found in the third girl child is a consequence of the long-term pre-pregnancy use of etidronate or underlying genetic predisposition. The data regarding maternal lumbar spine BMD values before her first pregnancy are lacking. Genetic factors may have a role in the development of PPSO, as patients may have a genetically determined low peak bone mass, so high calcium demands during the pregnancy can be a risk factor for PPSO and fractures [1].

In conclusion, the presented case shows that severe back pain during pregnancy and post-partum period may be indicative of pregnancy-associated spinal osteoporosis. The therapy with bisphosphonates that stimulate the formation of new bone tissue and reduce bone resorption together with calcium and vitamin D supplements substantially improved the BMD. No evidence of neonatal adverse effects was observed after long-term etidronate treatment before conception. The cause of low lumbar spine BMD found in the third child remains obscure, and the control DXA scans are recommended.

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