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REVIEW ARTICLE

Pregnancy-associated osteoporosis: a UK case series and literature review

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Abstract

Mini Abstract: Pregnancy-associated osteoporosis (PAO) is a rare syndrome affecting women during late pregnancy and the early postpartum period. We set out to review the clinical features of ten cases of PAO from a single UK centre. Patients had attended the Royal National Hospital for Rheumatic Diseases, Bath (RNHRD) between January 2000 and June 2016. The principal criterion for inclusion was the occurrence of low trauma fractures either during pregnancy or the immediate post-partum period. Data were obtained from retrospective review of medical notes. Bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry (Hologic ®Discovery system) at the lumbar spine and hip. Data pertaining to the pregnancy, as well as type and duration of treatment received, were reviewed. All ten cases presented with vertebral fractures. In four patients, no risk factors for fracture other than pregnancy or breastfeeding could be identified. Four patients were found to have vitamin D insufficiency at the time of diagnosis, and a further two patients had received treatment with low molecular weight heparin (LMWH). In one case, further investigation led to a diagnosis of osteogenesis imperfecta (OI) confirmed on genetic testing. In terms of treatment, eight out of the ten patients in this series received a bisphosphonate, most commonly risedronate due to its relatively short skeletal retention time. Clinicians should be aware of PAO, a rare but recognised complication of pregnancy. The condition should be especially considered in women presenting with new onset back pain in pregnancy or the postpartum period.

Keywords Fractures · Osteoporosis · Pregnancy

Introduction

Pregnancy-associated osteoporosis (PAO), also termed pregnancy and lactation-associated osteoporosis (PLO), is a rare syndrome of fragility fractures affecting women during late pregnancy and the early postpartum period. Formation of the fetal skeleton during pregnancy requires substantial calcium transfer. Whilst this is predominantly achieved through pregnancy adaptations such as increased intestinal calcium absorption, it can also lead to maternal skeletal resorption [1, 2], and comparison of BMD measurements before and after pregnancy suggests that pregnancy is associated with some degree of bone mass reduction in the mother [3, 4]. In mothers who go on to breastfeed, marked decreases in BMD are frequently observed [2]. Although this loss of BMD is temporary, with restoration of bone density generally occurring within 6–12 months of weaning [5], some women will experience fragility fractures during this period.

Management of these patients has a limited evidence base. Treatment with anti-resorptive therapy, whilst effective, is controversial and has the potential to cause harm to the fetus. Teriparatide has also been used in patients with PAO and may result in superior BMD gains compared with calcium and vitamin D alone [6]. In this article, we describe ten cases of PAO and briefly review the relevant literature.

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Materials and methods

Ten patients diagnosed with PAO were identified as having attended the RNHRD osteoporosis clinic between January 2000 and June 2016. The principal criterion for inclusion was the occurrence of low trauma fractures either during pregnancy or in the immediate post-partum period.

Data were obtained from retrospective review of records, including age, BMI, estimated dietary calcium intake and fracture details. Available haematological indices reflected the individual practice of different clinicians. These included serum hydroxyvitamin D (25(OH)D), serum bone alkaline phosphatase (BAP), serum corrected calcium, serum phosphate, parathyroid hormone (PTH), serum collagen type 1 cross-linked C-telopeptide (CTx), type 1 pro-collagen (N-terminal) (P1NP) and urinary N-telopeptide (NTx). Markers of bone resorption were measured following an overnight fast with blood samples collected between 8:30 and 10 am.

Bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry (Hologic ®Discovery system) at the lumbar region (L1-L4) and both hips. Radiographic fractures were further characterised using MRI. Data pertaining to the pregnancy, as well as type and duration of treatment received, were reviewed.

Cases

The features of all ten cases are summarised in Table 1 and described in detail below. Serial BMD values are shown in Table 2.

Case 1

A 31-year-old female, who initially presented with lower back pain during the third trimester of her second pregnancy. Two months after delivery, whilst still breastfeeding, she developed severe mid-thoracic and lumbar back pain. Radiographs, and subsequent MRI, confirmed a T12 vertebral fracture and height loss at T10, L1 and L5. 25(OH)D level was low (17 nmol/l); PTH and 24-h urinary calcium excretion were normal. DXA scanning revealed Z-scores of − 3.2 at the lumbar spine and − 1.9 at the femoral neck. Right iliac crest bone biopsy revealed thinning of the bone cortex with no increased osteoblastic or osteoclastic activity, and no evidence of osteomalacia. She commenced risedronate, which was continued for almost 5 years. Improvement in spinal BMD was seen after 2 years (lumbar spine Z-score − 2.5, femoral neck − 1.9). A repeat DXA scan at the end of treatment showed lumbar spine Z-score − 2.2 (14.3% improvement from baseline), femoral neck Z-score − 1.5 (5.8% improvement from baseline) and total hip Z-score − 1.7.

Case 2

A 29-year-old Moroccan female, resident in the UK for 18 months. Initial presentation was with back pain, 4 months after the birth of her first child whilst still breastfeeding. Imaging of the spine confirmed vertebral fractures at L1, L2 and L4, and height loss at T6, and T8–10. Lumbar spine and femoral neck Z-scores were − 3.7 and − 2.1, respectively. Serum 25(OH)D was low (9 nmol/l) with a mildly elevated PTH (13.8 pmol/l); other secondary causes of osteoporosis were excluded. She was commenced on vitamin D replacement and calcium supplementation. After 1 year, her lumbar spine Z-score was − 2.5 (20% improvement) and femoral neck Z-score − 1.8 (6.2% improvement). Due to the patient's wish to have another child, a bisphosphonate was not commenced.

Two years after her first pregnancy, the patient became pregnant again and developed further back pain during the third trimester and post-partum period. Updated spinal imaging showed new osteoporotic fractures at L3 and L5, and progressive biconcave wedging of L1 (Fig. 1). A repeat DXA scan following this second pregnancy showed Z-scores of − 2.4 at the lumbar spine and − 1.3 at the femoral neck. Oral risedronate was commenced. Two years later, an improvement in BMD was evident with Z-scores of − 1.5 at the lumbar spine and − 1.3 at the femoral neck. Shortly after this, the patient discontinued her bisphosphonate as she became pregnant with her third child. No further back pain or new fractures were noted during, or after, this subsequent pregnancy.

Case 3

A 19-year-old woman who developed new thoracic back pain after lifting her 4-month-old child. MRI of the thoracic spine showed bone oedema, fracture of the T6 vertebra and anterior wedging of T8 (Fig. 2). The clinical history revealed a background of numerous fractures during childhood, including left clavicle, scapula and humerus at the age of 4 years, right clavicle at age 5 and left ulna and radius at age 11. Her mother reported that as a toddler, she had complained of stiff and aching legs and continued to use a pushchair until the age of 4. However, she was later able to perform sports and activities alongside her peers. She reported a good diet with adequate dairy intake. There was no relevant family history. She was noted to have a low body mass of 18.5, but had been slim since childhood with no history of eating disorder, and regular menstruation following menarche at age 14. She was an ex-smoker.

Table 1 Demographic, fracture and treatment data

Case	Age at onset (years)	BMI (kg/m^2)	Parity at presentation	Pre-partum fracture	Family history fragility fracture	Risk factors (other than pregnancy)	Breastfeeding duration	Fracture site	Z-scores (lumbar, femoral neck, total hip)[a]	Treatment	Treatment duration (months)	Subsequent pregnancies with fractures
1	31	20.1	2	Y(wrist aged 11)	Grandmother osteoporosis	Low vit D	2 months	T10, T12, L1, L5	−3.2, −1.9, −2.0	Risedronate	55	N
2	29	26.6	1	N	No	Low vit D	10 months	T6, T8-T10, L1–2, L4	−3.7, −2.1, −2.4	Risedronate[b]	39	Y (L3, L5)
3	19	18.5	1	Y (several in childhood)	Yes (mother and grandfather)	Osteogenesis imperfecta, low vit D, BMI 18.5, ex-smoker	4 months	T6, T8	−7.8, −4.1, −4.4	Risedronate	56	N
4	37	22.1	1	N	Yes (mother vertebral – osteoporosis)	Low vit D, low dairy intake, LMWH use	Unknown	T7, T12, L2	−2.5, −2.1, −1.8	Risedronate	6 (on-going)	N
5	33	27.9	1	Y (both wrists, 1 leg as child)	Yes (mother wrist, grandmother hip)	None	5 months	T3-T12, L1-L5	−2.5, −2.0, −2.3	Risedronate	62	N
6	36	23.0	1	N	Unknown	None	6 months	T9-T11, L1-L5	−4.1, −2.3, −2.5	Risedronate	33	N
7	29	21.0	1	N	Unknown	None	Unknown	T10-T12, L1-L5	−3.6, −2.3	Risedronate[b] Ibandronate	116[c]	Y
8	37	24.1	3	N	No	LMWH use, ex-smoker	Unknown	Multiple thoracic vertebral fractures	−3.2, −2.8, −1.9	None	N/A	N/A
9	47 (?)	23.6	2	Y (wrist and thumb during teens)	No	Late menarche, ex-smoker	Unknown	T9, T11-L1	−2.7, −2.1, −2.1	Alendronate	120	N/A[d]
10	32	25.9	1	N	No	None	3 months	T9-T11	−1.5, 0.3, 0.1	No bisphosphonate	/	N

[a] Baseline DXA

[b] Risedronate started after second affected pregnancy

[c] Poor compliance with risedronate

[d] Presented some years after fractures occurred, timing not clear

Table 2 Changes in BMD on serial DXA scans

	DXA 1		Interval between scans 1 and 2	Treatment in interim	DXA 2		Interval between scans 2 and 3	Treatment in interim	DXA 3		Interval between scans 3 and 4	Treatment in interim	DXA 4	
Case number	Lumbar BMD (g/cm^2)	Femoral neck BMD (g/cm^2)			Lumbar BMD (g/cm^2)	Femoral neck BMD (g/cm^2)			Lumbar BMD (g/cm^2)	Femoral neck BMD (g/cm^2)			Lumbar BMD (g/cm^2)	Femoral neck BMD (g/cm^2)
1	0.689	0.62	26 months	Risedronate	0.766	0.623	28 months	Risedronate	0.788	0.656				
2	0.643	0.603	12 months	Calcium/vit D	0.772	0.640	10 months	Calcium/vit D	0.829	0.694	23 months	Risedronate	0.929	0.683
3	0.469	0.462	13 months	Risedronate	0.549	0.480	24 months	Risedronate	0.569	0.472	27 months	Risedronate	0.598	0.519
4	0.758	0.596	21 months	Risedronate	0.868	0.628								
5	0.773	0.682	12 months	Risedronate	0.832	0.665	12 months	Risedronate	0.870	0.718	19 months	Risedronate	0.903	0.726
6	0.587	0.572	21 months	Risedronate	0.780	0.631								
7	0.615	0.596	12 months	Calcium/vit D	0.675	0.597	13 months	Calcium/vit D	0.707	0.6	26 months	Calcium/vit D	0.720	0.613
8	0.684	0.578	16 months	Calcium/vit D	0.802	0.603	12 months	Calcium/vit D	0.862	0.596	18 months	Nil	0.876	0.6
9	0.682	0.546	25 months	Alendronate	0.738	0.581	8 years	Alendronate	0.650	0.564				
10	0.878	0.872	12 months	Calcium/vit D	0.923	0.867	2 years	Calcium/vit D	1.005	0.877				

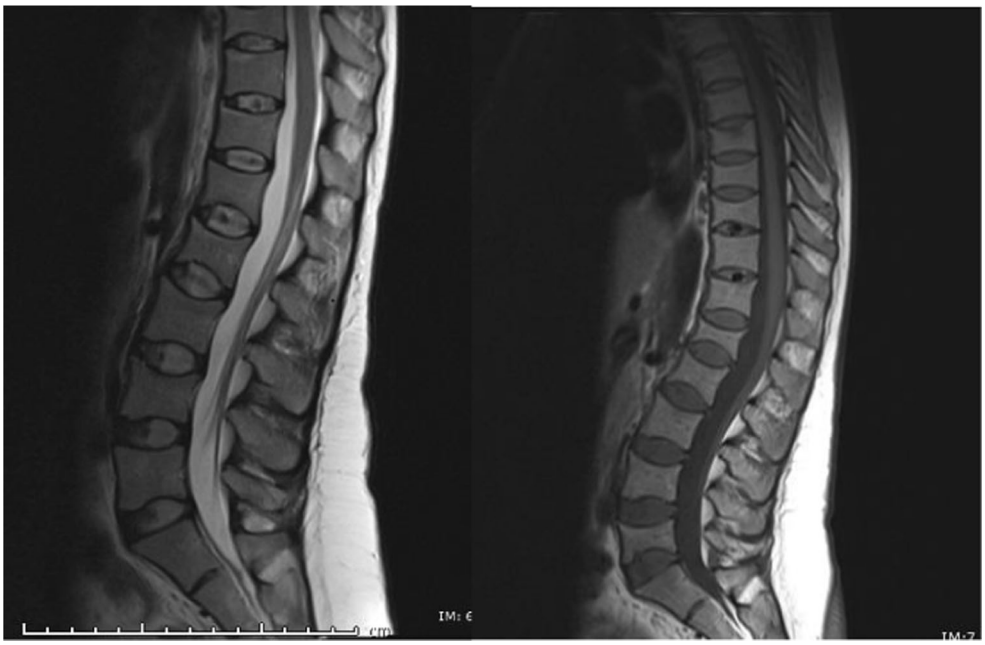

Fig. 1 Case 2. Vertebral fractures shown on MRI lumbar spine after first pregnancy (left) and MRI thoraco-lumbar spine after second pregnancy (right)

Clinical examination revealed joint hypermobility, brachycephaly and blue sclerae. A blood screen for secondary causes of osteoporosis was normal except for a low serum 25(OH)D (30 nmol/l). Urinary calcium excretion was reduced at 1.74 mmol/24 h. DXA scanning showed Z-scores of − 7.8 at the lumbar spine, − 4.1 at the femoral neck and − 4.4 at the total hip. An iliac crest bone biopsy showed focal osteoblast and osteoclast activity, no marrow fibrosis and no features of osteomalacia. The patient was commenced on risedronate, with calcium and vitamin D. Genetic testing detected a mutation of c.2314G>A in exon 38 of the *COL1A2* gene, confirming a diagnosis of osteogenesis imperfecta type I. Repeated DXA scanning 5 years later showed Z-scores of − 4.0 at the lumbar spine (27% improvement from baseline) and − 3.0 at the femoral neck (12% improvement). Risedronate was subsequently stopped as the patient wished to have more children.

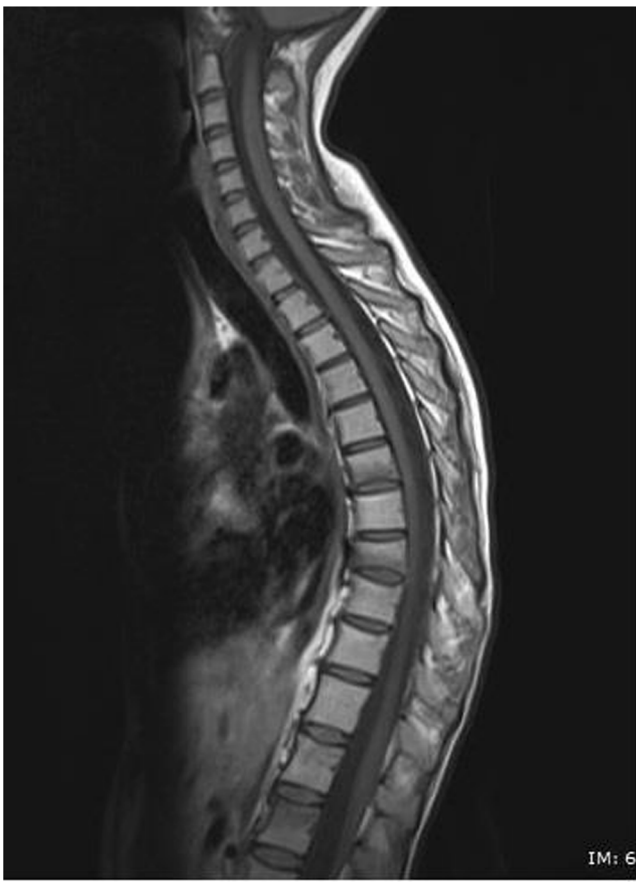

Fig. 2 Case 3. MRI thoracolumbar spine showing thoracic vertebral fractures

Case 4

This 38-year-old lady presented during her first pregnancy, with shortness of breath following a long car journey; investigations revealed a pulmonary embolism and she was treated with LMWH (dalteparin) twice daily. Twelve weeks postpartum, when leaning over to pick up her child, she developed pain in her thoracolumbar and mid lumbar regions. She was not breastfeeding. Imaging of the spine showed a superior endplate deformity at L2, and a T12 compression fracture, with a possible anterior wedge fracture at T7 (Fig. 3). A blood screen revealed a low serum 25(OH)D (20 nmol/l). A thrombophilia screen was negative. DXA scanning revealed Z-scores of − 2.5 at the lumbar spine, − 2.1 at the femoral neck and − 1.8 at the total hip. The patient was commenced on vitamin D replacement, calcium and risedronate. A repeat

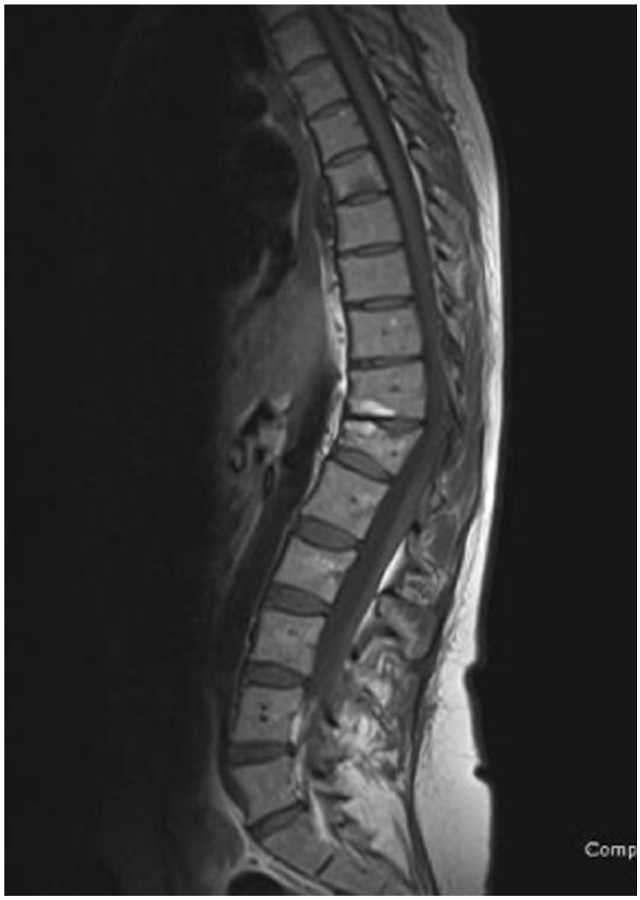

Fig. 3 Case 4. MRI spine showing thoracic and lumbar fractures mainly affecting L2, T7 and T12 vertebrae

DXA after 21 months of treatment showed significant improvement in BMD at all sites.

Case 5

A 33-year-old female, who developed persistent mid-lower back pain a few days after delivery of her first child. She had a background history of well controlled asthma, and three previous fractures involving both wrists and one leg in her childhood due to falls. She continued breastfeeding but noticed progressive pain, restricted mobility and 3 in. of height loss. Radiographs and MRI scanning confirmed multiple thoracic and lumbar vertebral compression fractures, with wedge or biconcave deformities in all but two of the thoracic vertebrae. A DXA scan showed Z-scores of − 2.5 at the lumbar spine and − 2.0 at the femoral neck. Secondary causes of osteoporosis were excluded (TSH, 25(OH)D and urinary calcium all normal). Bone biopsy was normal. Deoxypyrinoline/creatinine ratio was elevated at 19.2 and 14.3 nM Dpd/mM Cr 3 and 6 months, respectively, after fractures were confirmed. Urinary NTx/Cr ratio was normal at 31.5 nM BCE/mM Cr.

She was commenced on risedronate for 5 years, following which Z-scores were − 0.6 at the lumbar spine (24% improvement from baseline) and − 0.9 at the femoral neck (10% improvement). CTX was suppressed at 0.18 μg/L post-treatment. A DXA repeated after a further 5 years showed Z-scores of 0 at the lumbar spine and − 0.3 at the femoral neck.

Case 6

A 36-year-old female who became pregnant with twins following fertility treatment. Three weeks after delivery, she developed persistent back pain first noted on lifting her children out of the cot. Radiographs and MRI scanning confirmed multiple thoracic and lumbar fractures. A DXA scan showed Z-scores of − 4.1 at the lumbar spine and − 2.3 at the femoral neck. A blood screen including 25(OH)D was normal. The patient was commenced on risedronate with calcium and vitamin D. CTX was suppressed at 0.09 ug/L post-treatment. BMD measurement after almost 2 years of treatment showed Z-scores of − 2.3 at the lumbar spine (32.8% improvement) and − 1.7 at the femoral neck (10.3% improvement).

Case 7

A 29-year-old female, who presented with back pain 2 months after giving birth to her first child. Imaging of the spine revealed multiple thoracic vertebral fractures. A DXA scan showed Z-scores of − 3.6 at the lumbar spine and − 2.3 at the femoral neck. Other secondary causes of osteoporosis were excluded. The patient was commenced on calcium and vitamin D alone as she wanted more children. Four years later, she became pregnant again and delivered her child with no complications or fracture. Repeated BMD measurement did not show any significant change. Urinary NTx/Cr ratio showed no reduction at 38.1 nM BCE/mM Cr. She was commenced on risedronate, which was continued for a total of 10 years. Repeat BMD measurement after completing treatment unexpectedly showed some deterioration at the hip, with Z-scores of − 2.3 at the femoral neck (10.1% reduction) and − 1.8 at the lumbar spine (1.8% improvement); however, on further questioning, compliance was poor. Risedronate was subsequently stopped and changed to Ibandronate.

Case 8

A 37-year-old female who presented 2 weeks after an uncomplicated third pregnancy and normal delivery with symptoms of a high iliac venous thrombosis, treated with Tinzaparin. Six weeks later, she developed mid-lower back pain which radiated anteriorly. She attended the Emergency department; a CT scan showed vertebral fractures. Subsequent MRI spine revealed multiple osteoporotic deformities. DXA showed Z-scores of − 3.2 at the lumbar spine and − 2.8 at the femoral neck. There was no history of prior fractures, and the patient's

previous two pregnancies had been uncomplicated. She was an ex-smoker with a 15-year smoking history, normal age at menarche and had a good dietary calcium intake. Other secondary causes of osteoporosis were excluded. Tinzaparin was temporarily substituted for warfarin for a total of 6 months. A thrombophilia screen was negative. She remained on calcium and vitamin D for 2 years before discontinuing this due to intolerance. Subsequent DXA scans showed serial improvements in BMD (see Table 2). This patient presented again recently, at the age of 54, with an episode of sudden lumbar spine pain; no evidence of acute fracture was found and a repeat DXA scan showed stable BMD.

Case 9

This patient presented at the age of 47. She gave a history of low back pain which had started following the birth of her children back in the 1980s. She recalled specific episodes of acute back pain occurring after each of her deliveries, each of which took several weeks to settle. Lumbar spine radiographs at the time of referral showed superior endplate depression at a number of thoracic and lumbar vertebral levels. A nuclear medicine bone scan did not show active uptake within the spine, and a subsequent MRI scan confirmed biconcave fractures of T9 and possibly T10, with superior endplate collapse of T11, T12 and L1. A DXA scan showed Z-scores of − 2.7 at the lumbar spine and − 2.1 at the femoral neck. She had a past history of a wrist fracture in her teens and thumb fracture aged 10. She had had a delayed menarche (aged 15) and was an ex-smoker. Her mother had osteoporosis but no fractures. The patient was already on calcium and vitamin D at the time of referral. Blood tests revealed a normal calcium, phosphate, serum electrophoresis, urinary Bence Jones protein, plasma viscosity and TTG. FBC, TSH, U + E and LFTs were all normal; 25(OH)D was 33.1 μg/L (normal). Bone turnover markers showed low CTX (0.09 μg/L) and low P1NP (26 μg/L), considering the patient's premenopausal status. Alendronate was commenced. Repeat BMD 2 years later revealed Z-scores of − 2.1 at the lumbar spine and − 1.7 at the femoral neck, representing an 8.3% and 6.4% improvement at these sites. After 10 years of bisphosphonate treatment, repeat DXA showed stable hip BMD but a 12% decline at the lumbar spine, however as there had been no further fractures and CTX was fully suppressed (0.13 μg/L), a 3-year treatment holiday was recommended.

Case 10

A 32-year-old female presenting with back pain 1 month after delivering her first child. An MRI scan arranged by orthopaedics showed depression of the superior endplates of T9-T11 with intra-osseous protrusion of disc material (Fig. 4). Osteoporosis was suspected and the patient was referred to the bone clinic. A DXA scan showed low BMD at the lumbar spine, with Z-score − 1.5, and normal BMD at the hip (femoral neck Z-score 0.3). A nuclear medicine bone scan performed 9 months after delivery, by which time the patient's pain had significantly improved, showed no abnormal uptake within the vertebral column. The patient had breastfed for the first 3 months after delivery. No other risk factors were identified, in particular no prior fractures. Menarche was at the age of 14 and menses regular. Serum electrophoresis, IgA and anti-endomysial antibodies were normal. The patient commenced calcium and vitamin D, and her back pain continued to improve over time. A repeat DXA scan after an interval of 1 year showed improvement, with Z-scores of − 0.4 at the lumbar spine and 0.3 at the femoral neck. The patient gave birth to her second child 2 years later. As per the team's advice, breastfeeding duration was limited to 1 week. The DXA scan was repeated 9 months later (3 years from the baseline scan) and showed further improvement with Z-score − 0.3 at the lumbar spine and 0.4 at the femoral neck. No problems occurred following this second pregnancy.

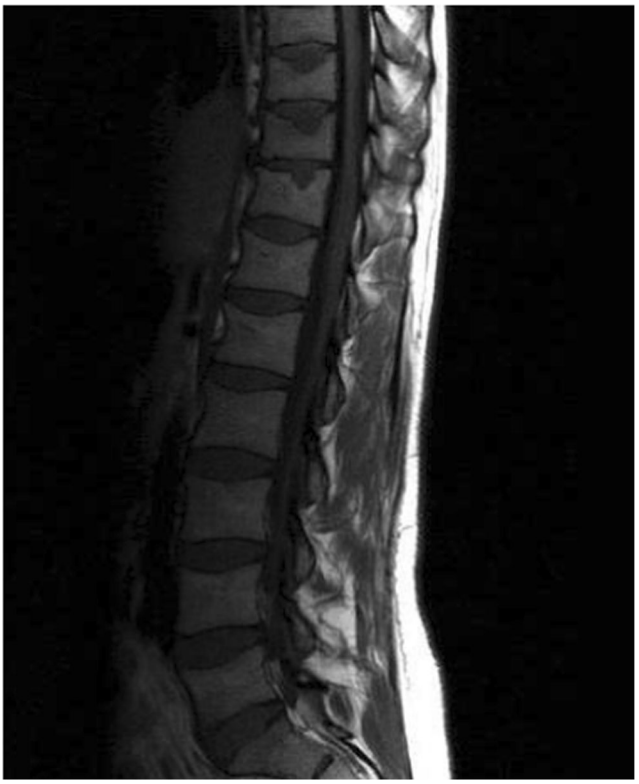

Fig. 4 Case 10. MRI showing superior endplate fractures of T9-T11

Discussion

We identified 10 patients with a diagnosis of PAO. All presented with vertebral fractures, which are the most frequently reported fractures in this condition [7]. In addition, all of our

patients presented with multiple fractures; this is in common with other published series such as a recent case-control study from Germany in which the mean number of fractures per patient was 3.3 [8]. Although hip fractures do occur during or following pregnancy, a distinction is made between fragility fractures occurring during this time and transient osteoporosis of the hip, which is considered a variant of complex regional pain syndrome type 1 [7]. The predominance of vertebral fractures in pregnancy-associated osteoporosis is thought to arise due to a combination of factors including bone loss occurring mainly at trabecular sites, and the mechanical effects of pregnancy on the spine such as weight gain and increased lumbar lordosis [2, 7]. In all of the cases reported here, Z-scores at the lumbar spine were lower than those at the hip.

Previously, the literature suggested that most women who sustain vertebral fractures as part of PAO do so in their first pregnancy, and that additional fractures in subsequent pregnancies are rare [7]. In keeping with this, in a recently published case series following up 107 women with PAO, 70% presented during or shortly after their first pregnancy; however, further fractures were reported in 20% of subsequent pregnancies [9]. In our series, two patients (cases 1 and 8) did not present with fractures until their second and third pregnancies, respectively. Another patient (case 2) went on to develop new vertebral fractures during her second pregnancy; this patient had multiple vertebral fractures at initial presentation, in keeping with the observation that a greater number of fractures at the time of PAO diagnosis may correlate with subsequent fracture risk [9]. The timing of presentation in relation to pregnancy and delivery was similar in our series to the much larger study published by Hadji et al. [8] in that the majority of patients (all but one) presented after delivery. Excluding case 9 who presented many years later, the median time from delivery to presentation in our series was 2 months, similar to the 3 months reported by Hadji et al. [8]

For four patients in our series, no risk factors for fracture other than pregnancy/breastfeeding could be identified. However, women presenting with PAO are frequently found to have other pre-existing conditions or factors which may have contributed to their low BMD and fractures [7, 10]. Unlike in the study by Hadji et al. [8], none of the women in our series had a BMI < 18 kg/m^2. Four of our patients were found to have insufficient levels of vitamin D at the time of diagnosis; however, vitamin D levels were normal in the other cases. In addition, two patients had received treatment with LMWH. Although the use of LMWH is thought to be less detrimental to the skeleton than unfractionated heparin [11], nevertheless there have been reports of women developing osteoporosis and vertebral fractures following the use of LMWH during pregnancy, even at prophylactic doses [12]. In vitro, dalteparin has been found to have a dose-dependent inhibitory effect on osteoblast proliferation [13]. Both of our patients received treatment-dose LMWH for treatment of VTE; one (case 4) did not have any identifiable risk factors for osteoporosis other than pregnancy, while the other (case 8) was an ex-smoker. Whether the LMWH exposure played any role in either patient's presentation, however, is uncertain.

One patient (case 3) presented with osteoporosis in the post-partum period, but further investigations led to a diagnosis of osteogenesis imperfecta (OI). Although her presentation was similar to that of the other cases, her history of a number of prior fractures during childhood suggested bone loss at a younger age. She also had mild characteristic physical features of OI. Other genetic conditions which have presented with fragility fractures during pregnancy include osteoporosis pseudoglioma syndrome [14] and loss of function mutations of *LRP5* [15]. The possibility of an underlying skeletal disorder is something that should always be considered in patients presenting with fractures during late pregnancy or the post-partum period.

The management of PAO is challenging, due both to a limited evidence base, and the fact that spontaneous improvement in BMD is known to occur (generally within 6–12 months) once pregnancy and lactation have been completed [7]. In this series, eight out of ten patients received treatment with a bisphosphonate after at least one of their pregnancies. Of the patients who did not receive a bisphosphonate, one (case 10) had only a moderately reduced Z-score (− 1.5) and the other had significant improvement of her back pain by the time of review and spontaneous improvement in BMD on follow-up DXA at 1 year.

Although the two approaches have not been directly compared, evidence suggests that the addition of anti-resorptive treatment in this setting may result in superior BMD gain compared with calcium and vitamin D supplementation alone [10]. O'Sullivan et al. (2006) found that patients with PAO had a 23% increase in spinal BMD over 2 years if they were treated with a bisphosphonate within 1 year of presentation [10]. The very long skeletal retention of bisphosphonates, and the fact that they can cross the placenta, has inevitably led to concerns regarding their use in women of childbearing potential. In two of the patients in our case series, the introduction of a bisphosphonate was delayed due to their stated wish to conceive again. Each was initially treated with calcium and vitamin D alone, with risedronate added following their second pregnancies, one of which was complicated by the occurrence of further fractures. The choice of risedronate for the majority of our patients was guided by the fact that its offset of action was thought to be more rapid than that of other oral bisphosphonates (alendronate and ibandronate), aiming to minimise any potential adverse effects on the fetus during a future pregnancy. However, it should be noted that, according to more recent data, the quicker recovery of bone turnover markers with risedronate may be due in part to less potent suppression of bone turnover during treatment [16]. One

patient (case 9) received alendronate, but was already in her late 40s at the time the drug was commenced. However, despite these concerns, to date, the evidence from the literature based on human exposure to these drugs either before or during pregnancy has been reassuring with respect to an absence of congenital malformations occurring without another explanation [17–19]. A 2011 literature review including 78 women exposed to bisphosphonates either before or during pregnancy concluded that in most cases, there was no evidence of significant harm to mother or fetus; however, a handful of cases of shortened gestational age, low birthweight and transient neonatal hypocalcaemia were observed [17].

Other drugs which have been used to treat PAO include strontium ranelate [20] and teriparatide [21, 22]. Zarattini et al. in 2014 reported the use of strontium ranelate to treat a patient with PAO presenting with multiple vertebral fractures; clinical response as judged by improvements in pain and the absence of further fractures was good, although the reported improvement in BMD will in part have reflected the skeletal retention of the strontium itself. Similarly, the use of teriparatide in pregnancy-associated osteoporosis presenting with vertebral fractures has been reported to produce both pain relief and substantial increases in BMD of up to 36% in the spine [21–23]. A recent observational study comparing 27 women with PAO who received 12 months of daily teriparatide injections with 5 untreated controls showed significantly greater increases in lumbar spine BMD in the treated group [6]. Nevertheless, controlled trials are lacking, and the optimal timing of teriparatide use in these women remains uncertain [7].

Strengths of this report include the description of a number of women with PAO treated at a single centre during routine clinical practice. As such, we are able to highlight the challenges and uncertainties around managing these patients. Weaknesses include the fact that investigations were not standardised, and that some relevant information (such as duration of breastfeeding) could not be ascertained from retrospective review of the clinical notes. One of our cases (case 9) did not present either during or immediately after pregnancy but a number of years later; due to the absence of imaging at the time of symptom onset, it is therefore impossible to be certain when the vertebral fractures occurred. However, as other authors have speculated [9], due to the rarity of PAO, it is likely that not all cases come to medical attention at the time, hence we decided to include this case of probable PAO in our series.

Conclusion

Women who present with back pain in late pregnancy or the post-partum period should always be evaluated for pregnancy-related osteoporosis. Traditional risk factors associated with osteoporosis should be assessed as they may be contributory, and other differential diagnoses (such as an underlying genetic disorder) should be considered. The use of bisphosphonates to treat these patients needs to be carefully considered, balancing the intended benefits of preventing subsequent fractures and disability against the potential risks of side effects and harm to future pregnancies.

Compliance with ethical standards

Conflicts of interest SH has received conference fee support from Lilly UK. FY has received funding for attending congresses and speaker fees from Pfizer, Novartis and Abbvie and grant/advisory board for Novartis. The other authors declare that they have no conflict of interest.

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References

1. Sanz-Salvador L, Garcia-Perez MA, Tarin JJ, Cano A (2015) Bone metabolic changes during pregnancy: a period of vulnerability to osteoporosis and fracture. Eur J Endocrinol 172:R53–R65
2. Kovacs CS (2014) Osteoporosis presenting in pregnancy, puerperium, and lactation. Curr Opin Endocrinol Diabetes Obes 21:468–475
3. Pearson D, Kaur M, San P, Lawson N, Baker P, Hosking D (2004) Recovery of pregnancy mediated bone loss during lactation. Bone 34:570–578
4. Moller UK, Vieth Streym S, Mosekilde L, Rejnmark L (2012) Changes in bone mineral density and body composition during pregnancy and postpartum. A controlled cohort study. Osteoporos Int 23:1213–1223
5. Kovacs CS (2016) Maternal mineral and bone metabolism during pregnancy, lactation, and post-weaning recovery. Physiol Rev 96:449–547
6. Hong N, Kim JE, Lee SJ, Kim SH, Rhee Y (2018) Changes in bone mineral density and bone turnover markers during treatment with teriparatide in pregnancy- and lactation-associated osteoporosis. Clin Endocrinol 88:652–658
7. Kovacs CS, Ralston SH (2015) Presentation and management of osteoporosis presenting in association with pregnancy or lactation. Osteoporos Int 26:2223–2241
8. Hadji P, Boekhoff J, Hahn M, Hellmeyer L, Hars O, Kyvernitakis I (2017) Pregnancy-associated osteoporosis: a case-control study. Osteoporos Int 28:1393–1399
9. Kyvernitakis I, Reuter TC, Hellmeyer L, Hars O, Hadji P (2018) Subsequent fracture risk of women with pregnancy and lactation-associated osteoporosis after a median of 6 years of follow-up. Osteoporos Int 29:135–142
10. O'Sullivan SM, Grey AB, Singh R, Reid IR (2006) Bisphosphonates in pregnancy and lactation-associated osteoporosis. Osteoporos Int 17:1008–1012
11. Compston J (2013) Skeletal effects of drugs. In: Rosen CJ (ed) Primer on the metabolic bone diseases and disorders of mineral metabolism, 8th edn. John Wiley & Sons, Hoboken
12. Ozdemir D, Tam AA, Dirikoc A, Ersoy R, Cakir B (2015) Postpartum osteoporosis and vertebral fractures in two patients treated with enoxaparin during pregnancy. Osteoporos Int 26:415–418

13. Handschin AE, Trentz OA, Hoerstrup SP, Kock HJ, Wanner GA, Trentz O (2005) Effect of low molecular weight heparin (dalteparin) and fondaparinux (Arixtra) on human osteoblasts in vitro. Br J Surg 92:177–183
14. Campos-Obando N, Oei L, Hoefsloot LH, Kiewiet RM, Klaver CCW, Simon MEH, Zillikens MC (2014) Osteoporotic vertebral fractures during pregnancy: be aware of a potential underlying genetic cause. J Clin Endocrinol Metab 99:1107–1111
15. Cook FJ, Mumm S, Whyte MP, Wenkert D (2014) Pregnancy-associated osteoporosis with a heterozygous deactivating LDL receptor-related protein 5 (LRP5) mutation and a homozygous methylenetetrahydrofolate reductase (MTHFR) polymorphism. J Bone Miner Res 29:922–928
16. Naylor KE, Bradburn M, Paggiosi MA, Gossiel F, Peel NFA, McCloskey EV, Walsh JS, Eastell R (2018) Effects of discontinuing oral bisphosphonate treatments for postmenopausal osteoporosis on bone turnover markers and bone density. Osteoporos Int 29:1407–1417
17. Stathopoulos IP, Liakou CG, Katsalira A, Trovas G, Lyritis G, Papaioannou N, Tournis S (2011) The use of bisphosphonates in women prior to or during pregnancy and lactation. Hormones (Athens) 10:280–291
18. Ornoy A, Wajnberg R, Diav-Citrin O (2006) The outcome of pregnancy following pre-pregnancy or early pregnancy alendronate treatment. Reprod Toxicol 22:578–579
19. Levy S, Fayez I, Taguchi N, Han JY, Aiello J, Matsui D, Moretti M, Koren G, Ito S (2009) Pregnancy outcome following in utero exposure to bisphosphonates. Bone 44:428–430
20. Zarattini G, Buffoli P, Isabelli G, Marchese M (2014) Pregnancy-associated osteoporosis with seven vertebral compression fractures, a case treated with strontium ranelate. Clin Cases Miner Bone Metab 11:139–141
21. Lampropoulou-Adamidou K, Trovas G, Stathopoulos IP, Papaioannou NA (2012) Case report: Teriparatide treatment in a case of severe pregnancy -and lactation- associated osteoporosis. Hormones (Athens) 11:495–500
22. Hellmeyer L, Boekhoff J, Hadji P (2010) Treatment with teriparatide in a patient with pregnancy-associated osteoporosis. Gynecol Endocrinol 26:725–728
23. Choe EY, Song JE, Park KH, Seok H, Lee EJ, Lim SK, Rhee Y (2012) Effect of teriparatide on pregnancy and lactation-associated osteoporosis with multiple vertebral fractures. J Bone Miner Metab 30:596–601