Successful treatment of gonadotropin releasing hormone induced severe pregnancy and lactation-associated osteoporosis with teriparatide

Sepideh Tahsini Tekantapeh
Alireza Khabbazi

Connective tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Address for correspondence:
Alireza Khabbazi, MD
Connective tissue Diseases Research Center
Tabriz University of Medical Sciences,
Tabriz, Iran
E-mail: khabbazia@tbzmed.ac.ir; dr.khabbazi@gmail.com

Summary

Pregnancy and lactation-associated osteoporosis (PLO) is characterized by significant changes in calcium and bone homeostasis and the subsequent occurrence of fragility fractures particularly in the vertebral bodies during third trimester of pregnancy or postpartum period. In this study, we present a case of PLO developed after gonadotropin releasing hormone (GnRH) therapy that had successfully been treated with teriparatide. A 34-year-old primiparous woman developed mechanical low back pain (LBP) in the 8th months of pregnancy. LBP exacerbated during the pregnancy and reached its maximum after delivery. Spinal radiographs and magnetic resonance imaging detected fractures in the T11-L2. Bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry and showed osteoporosis. Her past medical history was positive for receiving of GnRH one month before pregnancy. After the patient was diagnosed with PLO, breastfeeding was stopped. Calcium, vitamin D3 and teriparatide 20 μg/d were started. Ten days after the treatment, improvement in the patient's pain and mobility was observed. Ten months after the treatment, control BMD showed a significant increase in the lumbar and hip BMD. No new fractures developed during the treatment.

KEY WORDS: pregnancy and lactation-associated osteoporosis; pregnancy associated osteoporosis; gonadotropin releasing hormone; vertebral fracture; teriparatide.

Background

Pregnancy and lactation-associated osteoporosis (PLO) is characterized by significant changes in calcium and bone homeostasis and the subsequent occurrence of fragility fractures particularly in the vertebral bodies during the third trimester of pregnancy or postpartum period. Primarily, PLO affects primiparous women (1). Some determined risk factors include a history of osteoporosis, insufficiency fractures and PLO in first degree relatives, low body mass index (BMI), physical inactivity, preexisting vitamin D deficiency, insufficient calcium intake, increased parathyroid hormone related protein (PTHrP) and high bone turnover rates, the use of heparins, and smoking (2-6). This syndrome presents itself with disabling LBP and height reduction associated with vertebral osteoporotic fractures in third trimester or in postpartum period during breastfeeding (7).
The aim of the therapy is preventing new fractures, increasing BMD, and preventing chronic LBP development. Because of rarity and absence of controlled trial, there is no guideline for the treatment of PLO. The treatment options are limited to those practiced in case reports. Cessation of breastfeeding, calcium and vitamin D supplementation, and bisphosphonates are the most commonly reported therapies (7). Despite the efficacy of bisphosphonates in increasing BMD in patients with PLO, accumulation of these agents in the bone for several years and crossing the placenta raised the concern about the teratogenicity of this medications in the future pregnancies. Therefore, clinicians have considered alternative medications in the treatment of this condition. Parathyroid hormone (PTH) is an anabolic agent with a short half-life (8). Teriparatide, the human recombinant PTH in the treatment of postmenopausal osteoporosis with vertebral fractures, is very effective and a few case reports showed that teriparatide may be an effective therapy for PLO (9-17). Here we report a case of severe PLO which was successfully treated with teriparatide.

Case report

A 34-year-old primiparous woman with multiple vertebral fractures was referred to the Connective Tissue Diseases Research Center (CTDRC). She had given birth to a baby 2 months prior to her visit and had breastfed the baby for 2 months. It was in the 8th months of her pregnancy that she developed mechanical LBP. She denied any history of trauma. Her LBP exacerbated during the pregnancy and reach maximum after delivery. Since her pain was unbearable during movement, she could not get out of bed. She did not report night pain. Her pain did not improve by non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy. Her past medical history showed that she had received Gonadotropin releasing hormone (GnRH) for a month. Her menstrual cycles before pregnancy were normal. She had stopped contraceptive methods 23 months before her visit in order to conceive. Due to her lack of success in getting pregnant and her relatively old age, she became a candidate of in vitro fertilization (IVF) after 12 months and received GnRH. However, she became pregnant after one month without IVF and treatment with GnRH was discontinued. She had no history

of therapy with anticoagulants, corticosteroids, levothyroxine, anticonvulsants or any other medications that cause bone loss. She did not have any past or current history of smoking, alcohol consumption, or a maternal history of hip fractures. Daily calcium intake was 700 mg/d. Her familial history was significant only for osteoporosis in her mother. On physical examination, her vital signs were in normal range. Height, weight, and body mass index (BMI) were 155 cm, 54 kg, and 22.5 kg/m^2, respectively. Severe local tenderness was detected on upper lumbar vertebral. Spine motions in all directions were limited. Neurological examination was normal.

Spinal radiographs detected a loss of vertebral height in the T11-L2. Magnetic Resonance Imaging (MRI) exhibited multiple compression fractures in the same region (Figure 1). The bone mineral density (BMD) in the lumbar and pelvis anteroposterior views were measured using dual-energy X-ray absorptiometry (DXA) with Hologic QRD 4500 machine with least significant change of 0.022 gr/cm^2 in the lumbar area and 0.037 g/cm^2 in the pelvis area. DXA was consistent with osteoporosis (Table 1). Biochemical analyses were performed (Table 2). The only noticeable findings were a mild vitamin D insufficiency and a high bone specific alkaline phosphatase (BAP). Based on the progressive clinical course, imaging findings, and exclusion of other causes of osteoporosis, the patient was diagnosed with PLO.

After the diagnosis of PLO, breastfeeding was stopped. Calcium 1000 mg/day, vitamin D3 800 IU/day, teriparatide 20 µg/day, celecoxib 200-400 mg/d, and nortriptyline 20 mg/d were started. Ten days after the treatment improvement in the patient's pain and mobility was observed. Two month after the treatment, the patient could get up and do her daily activities. Four months later celecoxib was discontinued. Ten months after the treatment, the patient was pain-free and follow-up BMD showed significant increase in the lumbar and hip BMD (Table 2). We had planned to continue the teriparatide for up to 18 months. Due to the patient's desire for future pregnancy, we decided not to use antiresorptive agents after discontinuing teriparatide; and we followed her disease management with serial BMD and calcium and vitamin D supplementation.

Discussion

In this study, the presented case had developed severe LBP and multiple vertebral fractures in the 8th months of her pregnancy. Low calcium intake during pregnancy, mild vitamin D insufficiency, a history of osteoporosis in her mother and probably treatment with GnRH were the risk factors of PLO in this case. Disabling LBP in the third trimester of pregnancy or the early postpartum period is the main manifestation of PLO. However, LBP in the perinatal period is very common. In Ansari et al. report prevalence of LBP during pregnancy was 57% (18). Pregnancy related LBP and pelvic girdle pain (PGP) are the most common causes of lumbopelvic pain (19). Laxity and poor muscle function of the back and pelvis because of hormonal and physiological changes and increase in body mass during pregnancy are the main causes (19). Lumbopelvic pain usually begins in the 18th weeks of

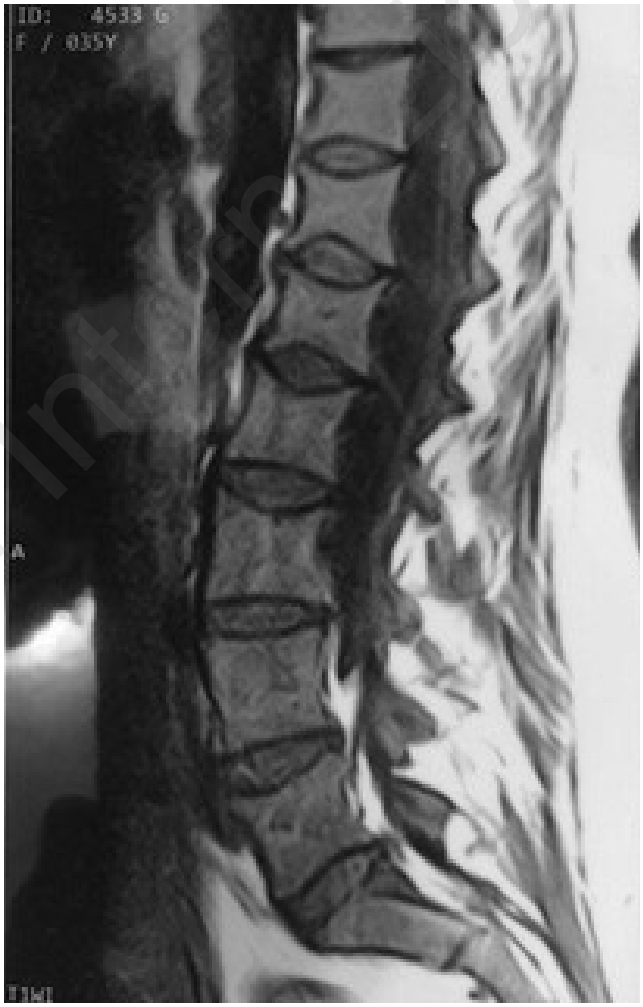

Figure 1 - Sagittal MRI of spine revealed vertebral fractures at T11-12 and L1-2.

Table 1. BMD before and 6 months after treatment.

	L1-4		Femur neck	
	Before treatment	**After treatment**	**Before treatment**	**After treatment**
T-score	-3.8	-1.9	-2.8	-2.3
Z-score	-3.7	-1.9	-2.7	-2.1
BMD (g/cm^2)	0.630	0.834	0.535	0.599

BMD: Bone mineral densitometry

Table 2. Biochemical markers before and 6 months after treatment.

Laboratory parameter	Before treatment	After treatment	Normal range
Hemoglobin (g/L)	11.7	12.5	12-14.5
ESR (mm/h)	13	10	0-20
CRP (mg/dL)	6.5	5.4	0-10
Creatinine (mg/dL)	0.9	1	0.6-1.1
Uric acid (mg/dL)	5.3	6.4	5-6.5
Calcium (mg/dL)	9.2	8.8	8.5–10.2
Phosphorus (mg/dL)	3.8	3.9	2.5–4.5
ALP (IU/L)	320	250	100–340
25 OH vitamin D (ng/mL)	27.2	32.8	10-30
24 h urine calcium (mg/dL)	167	205	100-250
Intact PTH (pg/mL)	36.1	52	10–66
TSH (μIU/mL)	3.3	2.7	0.35-5.58
BAP (mg/L)	49.7	31.1	3.8–22.6

ESR: Erythrocyte sedimentation rete; CRP: C-reactive protein; ALP: Alkaline phosphatase; PTH: Parathyroid hormone; Thyroid stimulating hormone (TSH); Bone specific alkaline phosphatase (BAP)

pregnancy and maximized in the weeks 24-36 (19). These patients generally experience moderate to severe bilateral pain in the lumbosacral area, radiating to the buttocks and thighs. Other causes of mechanical LBP that are more common in pregnant women are lumbar disk herniation, spondylolisthesis, and pubic symphysis diastasis (19). PLO is a rare cause of back pain during pregnancy. PLO occurs most frequently during the first pregnancy and back pain appear in third trimester or after delivery. Height loss is another important manifestation of PLO (20). The fractures are most commonly seen in the lower thoracic and lumbar spine. BMD loss in the spine is more severe and more common than other parts of skeleton (20). It is estimated that 33% of patients with PLO and fractures may develop another fracture (21). There are no exact diagnosis criteria for PLO. Diagnosis is based on the development of severe back pain in the third trimester of pregnancy or lactation period in the absence of other underlying causes, imaging (radiography or MRI) evidence of compression fracture and low BMD in the densitometry (15, 20). Although not defined as diagnostic criteria, the exclusion of other causes of osteoporosis and progressive clinical course are helpful for diagnosis (20).

Bone turnover increases during pregnancy and lactation. During the third trimester of pregnancy 110-120 mg/kg/d calcium is transported from the maternal bones to the fetus and mother's BMD decrease in the range of 2-4% (22). Calcium loss during lactation is more than that of pregnancy and reaches 300 mg/day (23). BMD loss in lactating women approximates 1-3% per month (23). Prolactin and parathyroid-related peptide (PTHrP) are key modulators of bone metabolism during pregnancy and lactation (22). Breastfeeding stimulates secretion of prolactin which in turn suppresses production of the gonadotropins and by this way leading to low levels of the estradiol. In addition, prolactin increase the production of PTHrP (23). Low estradiol and PTHrP act synergistically to increase bone resorption (23). Non-physiologic bone loss during pregnancy and lactation leads to PLO.

The presented case developed PLO after treatment with GnRH. The patient had no other known risk factor of PLO. We did a systematic and hand search of the literature and electronic databases, including MEDLINE (1966–May 2006), EMBASE and google scholar for studies published between 1990 and March 2017. Search terms were: "pregnancy and lactation associated osteoporosis" OR "pregnancy associated osteoporosis", AND "gonadotropin releasing hormone" OR "*in vitro* fertilization" OR "IVF". The search resulted in 2 cases of PLO after IVF. In Cho et al. report, one of the patients with PLO became pregnant after IVF (12). Lampropoulou-Adamidou et al. reported a 40-year-old woman with PLO conceived through IVF (11). Our patient had been treated with GnRH for one month and became pregnant without IVF. After popularization of GnRH therapy for delaying puberty and management of female disorders that are dependent on estrogen productions like endometriosis, concerns developed about the possibility of GnRH induced bone loss. The hypoestrogenic state which develops in patients treated with GnRH can accelerate bone loss. It is reported that a six-months therapy with GnRH causes 8.2% decrease in the lumbar bone density (24). Kaya et al. reported that 56.5% of children with central precocious puberty treated with GnRH for at least 12 months developed osteopenia (25). However, no data exists on the effects of shorter courses of GnRH therapy on bone density.

Therapy with teriparatide for 10 months caused a dramatic relief of LBP, a 33% increase in the lumbar BMD and decrease in BAP in our patient. Previous reports showed that calcium and vitamin D supplementation combined with stopping breastfeeding could increase lumbar BMD by 6% in 8 months and 9.5% in 2-4 years (21). A few case reports showed that teriparatide is an effective medication for the treatment of PLO. We identified all studies on teriparatide in patients with PLO by a systematic search of the literature and electronic databases, including MEDLINE (1966-May 2006), EMBASE and google scholar for studies published

Table 3. Summary of published cases of PLO treated with teriparatide.

Study	Age (years)	Ethnicity	Parity	Site of fracture	Duration of treatment (months)	Percent of BMD increase in the lumbar area	Time to improve back pain	Fracture recurrence during treatment and follow up
Stumpf et al. 2007 (9)	32	-	-	Thoracic and lumbar spine	6	42.5	3 months	No
Hellmeyer et al. 2010 (10)	40	Caucasian	G4P2	Thoracic and lumbar spine	18	36	-	No
Lampropoulou-Adamidou et al. 2012 (11)	40	Caucasian	G1P1	Thoracic and lumbar spine	13	24.4	Several days	No
Choe et al. 2012 (12)	36	Asian	G2P2	Thoracic and lumbar spine	18	14.5	3 months	No
Choe et al. 2012 (12)	32	Asian	G4P1	Thoracic and lumbar spine	18	25	5 months	No
Choe et al. 2012 (12)	30	Asian	G1P1	Thoracic and lumbar spine	4	-	1 month	No
Lee et al. 2013 (13)	39	Asian	G1P1	Lumbar spine	4	11.6	-	No
Coskun Benlidayi et al. 2014 (14)	25	Caucasian	G1P1	Thoracic and lumbar spine	6	16.7	3 months	No
Winarno et al. 2014 (15)	28	-	-	Thoracic and lumbar spine	18	-	-	No
Polat et al. 2015 (16)	23	Caucasian	G1P1	Thoracic and lumbar spine	18	27	2 months	No
Niculescu et al. 2016 (17)	29	Caucasian	G2P2	Thoracic and lumbar spine	6	12.1	3 months	No
Tahsini et al. 2017	34	Caucasian	G1P1	Thoracic and lumbar spine	10	33	10 days	No

PLO, pregnancy and lactation associated osteoporosis
BMD, bone mineral density
G, gestation
P, parity

between 1990 and March 2017. Search terms were: "pregnancy and lactation associated osteoporosis" OR "pregnancy associated osteoporosis", AND "teriparatide" OR "parathyroid hormone". The search resulted in 9 case reports and 11 cases of PLO treatment by teriparatide. Table 3 shows the published cases of PLO treated with teriparatide. In the reported cases, teriparatide was used with a dose of 20 μg/day for 4-18 months. In the reported cases, back pain improved in several days to 5 months. BMD increased 11.6-42.5% in the lumbar spine. Fracture recurrence during treatment and follow up did not occur. Teriparatide was also effective in treating resistant cases of PLO. Winarno et al. reported a 28-year-old woman with progressive osteoporotic spine fractures which were resistant to bisphosphonates (15). Despite 3 years of treatment with alendronate and ibandronate, additional end plate fractures had happened. After treatment with PTH for 18 months, BMD increased and no further fractures happened. Data regarding the optimal duration of therapy with teriparatide in PLO are limited. However, in most of the reported cases treatment with teriparatide was continued for 18 months (10, 12, 15, 16).

The main limitations of our report are the scarcity of data on the occurrence of fragility fractures after GnRH treatment, and a short duration of treatment with GnRH compared to previous reports. For this reason, attribution of PLO to GnRH should be done cautiously.

In conclusion treatment with GnRH may be a risk factor for PLO. Treatment of severe PLO using teriparatide combined with calcium and vitamin D supplementation and stopping of breastfeeding may be effective ways of increasing bone density and preventing new fractures.

Acknowledgements

We are grateful to Dr. L. Khabbazi for editing this manuscript.

Conflicts of interest

Authors declare no conflict of interests for this article.

References

1. Smith R, Athanasou NA, Ostlere SJ, Vipond SE. Pregnancy-associated osteoporosis. QJM. 1995;88(12):865-878.
2. Kovacs CS. Calcium and bone metabolism in pregnancy and lactation. J Clin Endocrinol Metab. 2001;86(6):2344-2348.
3. Barbour LA, et al. A prospective study of heparin-induced osteoporosis in pregnancy using bone density. Am J Obstet Gynecol. 1994;170(3): 862-869.
4. Dahlman TC. Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. Am J Obstet Gynecol. 1993;168(4):1265-1270.
5. Dunne F, Walters B, Marshall T, Heath D. A. Pregnancy associated osteoporosis. Clinical Endocrinology. 1993;39(4):487-490.
6. O'Sullivan SM, Grey AB, Singh R, Reid IR. Bisphosphonates in pregnancy and lactation-associated osteoporosis. Osteoporosis International. 2006;17(7):1008-1012.
7. Rabia Terzi, Hasan Terzi, Tülay Özer, and Ahmet Kale. A Rare Cause of Postpartum Low Back Pain: Pregnancy- and Lactation-Associated Osteoporosis. Biomed Res Int. 2014;2014:287832.
8. Quattrocchi E, Kourlas H. Teriparatide: a review. Clin Ther. 2004;26 (6):841-854.
9. Stumpf UC, Kurth AA, Windolf J, Fassbender WJ. Pregnancy-associated osteoporosis: an underestimated and underdiagnosed severe disease. A review of two cases in short- and long-term follow-up. Adv Med Sci. 2007;52:94-97.
10. Hellmeyer L, Boekhoff J, Hadji P. Treatment with teriparatide in a patient with pregnancy-associated osteoporosis. Gynecol Endocrinol. 2010;26 (10):725-728.
11. Lampropoulou-Adamidou K, Trovas G, Stathopoulos IP, Papaioannou NA. Case Report: Teriparatide treatment in a case of severe pregnancy -and lactation- associated osteoporosis. Hormones (Athens). 2012;11 (4):495-500.
12. Choe EY, et al. Effect of teriparatide on pregnancy and lactation-associated osteoporosis with multiple vertebral fractures. J Bone Miner Metab. 2012;30(5):596-601.
13. Lee SH, et al. A case of teriparatide on pregnancy-induced osteoporosis. Journal of Bone Metabolism. 2013;20(2):111-114.
14. Coskun Benlidayi I, Sarpel T, Guzel R. Short-term treatment experience with teriparatide in pregnancy- and lactation-associated osteoporosis. J Obstet Gynaecol. 2014;34(8):736.
15. Winarno AS, Kyvernitakis I, Hadji P. Successful treatment of 1-34 parathyroid hormone (PTH) after failure of bisphosphonate therapy in a complex case of pregnancy associated osteoporosis and multiple fractures. Z Geburtshilfe Neonatol. 2014;218(4):171-173.
16. Polat SB, Evranos B, Aydin C, Cuhaci N, Ersoy R, Cakir B. Effective treatment of severe pregnancy and lactation-related osteoporosis with teriparatide: case report and review of the literature. Gynecol Endocrinol. 2015;31(7):522-525.
17. Niculescu DA, Pintoiu D, Dusceac R, Barbu CG, Poiana C. Rapid response to teriparatide in a postpartum osteoporosis case associated with nardroparine treatment during pregnancy. AACE Clinical Case Reports Rapid Electronic Articles in Press. 2016
18. Ansari NN, Hasson S, Naghdi S, Keyhani S, Jalaie S. Low back pain during pregnancy in Iranian women: Prevalence and risk factors. Physiother Theory Pract. 2010;26(1):40-48.
19. Casagrande D, Gugala Z, Clark SM, Lindsey RW. Low Back Pain and Pelvic Girdle Pain in Pregnancy. J Am Acad Orthop Surg. 2015;23(9): 539-549.
20. Smith R, Stevenson JC, Wordsworth BP. Osteoporosis of pregnancy. Lancet. 1985;1(8439):1178-1180.
21. Phillips AJ, Ostlere SJ, Smith R. Pregnancy-associated osteoporosis: does the skeleton recover? Osteoporos Int. 2000;11:449-454.
22. Sanz-Salvador L, García-Pérez MÁ, Tarín JJ, Cano A. Bone metabolic changes during pregnancy: a period of vulnerability to osteoporosis and fracture. European Journal of Endocrinology. 2015;172(2):R53-65.
23. Kovacs CS. Calcium and bone metabolism disorders during pregnancy and lactation. Endocrinol Metab Clin North Am. 2011;40(4):795-826.
24. Adashi EY.) Long-term gonadotropin-releasing hormone agonist therapy: the evolving issue of steroidal "add-back" paradigms. Keio J Med. 1995;44(4):124-132.
25. Kaya A, Cayir A, Turan M, Ozkan B. An Examination of the Effects of Leuprolide Acetate Used in the Treatment of Central Precocious Puberty on Bone Mineral Density and 25-Hydroxy Vitamin D. West Indian Med J. 2015;64(2):104-107.