

# Pregnancy- and lactation-associated osteoporosis

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## Abstract

Pregnancy- and lactation-associated osteoporosis is a rare syndrome of spontaneous fractures occurring in late pregnancy or lactation. Early diagnosis and management is essential, because of the severity of the morbidity associated with these fractures. Prior to therapy, other reversible causes of osteoporosis should be excluded through adequate investigation. Treatment includes cessation of breastfeeding, the provision of adequate pain relief, and the use of specific osteoporosis drugs, preferably those with short-term bone retention. Although there is no persuasive evidence that calcium and vitamin D requirements increase during pregnancy or lactation compared to the non-pregnant woman of childbearing age, it is advisable to ensure that women are vitamin D replete during pregnancy and lactation.

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## Introduction

Osteoporosis, a condition that is usually associated with ageing and which is found in postmenopausal women, can present during pregnancy and lactation. A syndrome of spontaneous fractures that occurred in late pregnancy or lactation was first reported by Albright and Reifenstein in 1948. In 1955, Nordin and Roper published four cases.<sup>1</sup> By 2006, there were 100 cases in the literature.<sup>2</sup> We discuss two patients who developed multiple vertebral fractures during pregnancy and lactation. This paper encompasses a review of the current knowledge on calcium and vitamin D metabolism in pregnancy, as well as the aetiology, clinical features and treatment of this condition. Focus is given to the clinical syndrome of pregnancy- and lactation-associated osteoporosis. A summary is provided of other causes that could be responsible for bone loss in pregnancy.

## Case 1

A 30-year-old woman presented 11 weeks after delivering her first child with a history of acute onset of back pain which had started seven days postpartum. She felt the pain while lifting her baby. There was a loud "crack", accompanied by excruciating back pain. The patient was breastfeeding.

Her 58-year-old mother had suffered vertebral fractures. There were no other clinical risk factors for osteoporosis.

Magnetic resonance imaging (MRI) (Figure 1) showed acute vertebral compression fractures at T11, T12, L1, L2, L3 and L4. The dual-energy x-ray absorptiometry (DXA) findings are shown in Table 1.

## Investigations

The patient's serum calcium and phosphate, 24-hour urine calcium, parathyroid hormone (PTH), 25-hydroxyvitamin D (25-OH D), liver function and urea and electrolytes were all normal.

## Treatment

Breastfeeding was discontinued. Calcium (500 mg daily) and vitamin D (800 IU) daily were given, as well as alendronate 70 mg weekly for six months, followed by risedronate 35 mg weekly for 28 months. The decision to change to risedronate was made because it has less potent binding to hydroxyapatite and octacalcium phosphate, and therefore shorter retention in bone than alendronate. This profile was thought to be preferable for a younger patient. At follow-up DXA after 12 and 24 months of risedronate, the BMD in the hips remained stable. There was a significant increase in lumbar spine density. No further fractures occurred and the pain settled over four months.



Figure 1: Spinal fractures (Case 1)

Table I: DXA findings (Case 1)

DXA scans	Z-scores
L1-L4	-2.7
Femoral neck	-2.4
Total femur	-2.3

### Case 2

A 23-year-old breastfeeding woman presented four weeks after the delivery of her first child with a history of spontaneous onset of severe back pain.

There was no history of any risk factors for osteoporosis, other than that her paternal grandmother had osteoporosis.

MRI (Figure 2) showed acute vertebral fractures at T6, T7, T8, T9, T10, T11, T12 and L1. The DXA findings are shown in Table II.

### Investigations

The patient's serum calcium and phosphate, 24-hour urine calcium, PTH, 25-OH D, liver function and urea and electrolytes were all normal.

### Treatment

Breastfeeding was stopped. Calcium (500 mg daily) and Vitamin D (800 IU daily) were given, as well as risedronate 35 mg weekly for 12 months. After 12 months



Figure 2: Spinal fracture (Case 2)

Table II: DXA findings (Case 2)

DXA scans	Z-scores
L1-L4	-2.9
Femoral neck	-1.7
Total femur	-2.1

of risedronate, the bone density increased 13.4% in the spine and 3.4% in the total femur. The back pain progressively improved over the next three months. A further pregnancy is being planned.

### Discussion

#### Calcium homeostasis during pregnancy and lactation

Pregnancy and lactation is a special period in a woman's life, when calcium demands are increased to accommodate the requirements of the growing foetus and the losses that occur in breastmilk during lactation. Several excellent reviews on calcium and vitamin D requirements during pregnancy and lactation have been published recently,<sup>3-6</sup> and the reader is referred to these for more details.

During pregnancy, the mother must increase her calcium retention to allow for the calcium needs of the growing foetal skeleton, which at birth contains approximately 30 g of calcium. Most of the skeletal growth occurs during the third trimester, during which roughly 200-250 mg calcium per day is required. It

appears that these increased demands are met mainly through increased intestinal calcium absorption, which doubles during pregnancy. At present, the mechanisms through which this is achieved are unclear, although increased 1,25-dihydroxyvitamin D concentrations, together with placental lactogen, may play a role.

During lactation, the increased demand for calcium is even higher than during pregnancy. Approximately 300 mg/day is required to replace the calcium that is secreted in the breastmilk. The mechanisms through which this demand is met are different to those which take place during pregnancy. During lactation, intestinal calcium absorption returns to pre-pregnancy levels and urinary calcium excretion decreases. However, because of low oestrogen and high parathyroid hormone-related protein (PTHrP) concentrations that are secreted by the breast tissue, bone resorption is markedly increased. This results in a large calcium efflux from bone, which is then available for secretion in the breastmilk.

The consequence of the mobilisation of calcium from bone during lactation is a rapid and consistent fall in bone mass, particularly at those sites that are high in trabecular bone, such as the vertebral bodies. It has been estimated that losses are between 5% and 14% of bone mineral content (BMC) or BMD.<sup>7,8</sup> These losses begin rapidly as soon as lactation commences and persist for the duration of lactation. During weaning, bone mass rapidly returns to normal, recovering at 0.5-2% a month. Some researchers have suggested that pregnancy and lactation may be associated with a higher prevalence of osteoporosis in later life, but this has not been substantiated in other studies.

### The effect of calcium supplementation

As far as bone health is concerned, there is little evidence to support the contention that calcium supplementation influences the rate or extent of bone loss that occurs during pregnancy and lactation,<sup>5,9</sup> or the recovery that takes place during weaning.<sup>10</sup> Furthermore, calcium supplements do not appear to alter breastmilk calcium concentrations.<sup>11</sup> Even in populations that consume very low calcium intakes (a mean of 280 mg/day), there is no evidence that calcium supplementation reduces bone loss during lactation or the rate of bone gain in response to weaning.<sup>9</sup> Although calcium intakes appear to play little role in bone health during pregnancy and lactation, there is accumulating evidence that in developing communities with habitually low calcium intakes, calcium supplementation reduces the prevalence of gestational hypertension and pre-eclampsia, the risk of preterm deliveries and neonatal mortality.<sup>4,12</sup>

### Vitamin D requirements during pregnancy and lactation

Recently, there has been considerable discussion about the definition of vitamin D deficiency and the measurement of vitamin D sufficiency. In response to the uncertainties within the literature and the wide range of claims that have been made by health professionals about the importance of vitamin D in preventing cancer, immunological and autoimmune disorders and hypertension and diabetes, the Institute of Medicine (IOM) in the USA set up a task team to review the literature and to make recommendations on the dietary requirements for calcium and vitamin D throughout the life cycle. The report was released as a draft towards the end of 2010 and the final report was published in 2011.<sup>13</sup>

The report confirms the value of determining serum 25-OH D as an indicator of vitamin D status, because it reflects both dietary intake and the endogenous cutaneous production of vitamin D. The panel concluded that a serum 25-OH D concentration of 20 ng/ml (50 nmol/L) is indicative of vitamin D sufficiency, while a value < 12 ng/ml (30 nmol/L) is indicative of vitamin D deficiency. Further, the panel concluded that there is no evidence to suggest that pregnant and lactating women have greater vitamin D requirements than other women.

Both animal and human studies suggest that the foetus does not require vitamin D for its intrauterine growth or calcium homeostasis.<sup>14</sup> However, postnatally, the infant is very dependent on its vitamin D metabolite store at the time of delivery and on acquiring vitamin D through cutaneous synthesis, fortified milk formula, breastmilk or supplements to maintain its vitamin D status during infancy. At birth, neonatal 25-OH D concentrations correlate with those of the mother, thus vitamin D sufficiency in the mother during pregnancy results in a neonate being protected from vitamin D deficiency for the first weeks of postnatal life. On the other hand, Vitamin D deficiency in the mother predisposes the neonate to neonatal hypocalcaemia and to rickets during infancy.

In many countries, numerous articles have highlighted the high prevalence of vitamin D deficiency in women of childbearing age and during pregnancy, especially in Europe in dark-skinned immigrants and in the Middle East.<sup>15,16</sup> Data for South African women are not available. However, information on adolescent black and white children in Johannesburg suggests that vitamin D deficiency is uncommon in that age group, and thus by extrapolation, is probably uncommon in healthy adult women.<sup>17</sup>

The IOM recommends a dietary vitamin D intake of 600 IU/day for all women of childbearing age, irrespective of whether or not they are pregnant or lactating. This recommendation assumes that limited or no skin synthesis of vitamin D occurs, which is unlikely to be the situation in South Africa. However, in the South African situation, few foods are vitamin D fortified, thus vitamin D sufficiency can only be achieved through cutaneous vitamin D synthesis or vitamin D supplements. Therefore, the National Osteoporosis Foundation of South Africa recommends a vitamin D supplement of 800-1000 IU/day, which is very similar to the more recently released IOM recommendations for pregnant and lactating women in South Africa. This is probably appropriate as it will ensure vitamin D sufficiency in pregnant and lactating women without the need for an individual assessment of vitamin D status, which is expensive at present, and without insight into the vitamin D status of women of childbearing age in relation to geographical region, body composition, season or ethnicity.

In summary, currently, there is no persuasive evidence to suggest that calcium or vitamin D requirements increase during pregnancy or lactation, compared to the requirements of non-pregnant women of childbearing age. However, it would be prudent to ensure that women are vitamin D replete during pregnancy and lactation, so as to reduce the risk of vitamin D deficiency in the young infant. There is also no evidence to suggest that calcium or vitamin D supplements above the normal requirements reduce the risk of fractures and low bone mass during pregnancy and lactation, or speed the recovery of bone mass during weaning.

### Clinical presentation

As in the two cases described here, the most common presentation is that of a painful vertebral fracture or fractures that occur suddenly in late pregnancy or during lactation. Usually, they occur in a first pregnancy, and although it has been described,<sup>1</sup> do not generally recur in subsequent pregnancies.<sup>1,18</sup>

### Aetiology

The aetiology of this condition still remains unclear. In most instances, as these fractures occur in women who have no history of having had bone density assessments, or having been suspected of having compromised bone strength,<sup>1,18</sup> it is not certain whether the fractures occur because of increased bone resorption occurring during pregnancy and lactation, or whether the bone quality was compromised prior to the pregnancy. A mother had vertebral fractures in one of the two cases presented in this report. Dunne et al<sup>19</sup> report on there

being a greater incidence of fractures that occur in the mothers of 35 patients with pregnancy-associated osteoporosis than in the mothers of controls. Genetic factors could therefore be implicated.

It has been suggested that raised PTHrP may play a role in increasing bone resorption.<sup>1,18</sup> As described above, PTHrP is raised during late pregnancy and lactation. This, together with low estradiol levels during lactation, could significantly increase bone loss. The fact that in most instances the bone loss reverses after pregnancy supports the postulate that bone loss is a consequence of changes in pregnancy which increase bone resorption.<sup>3,20</sup>

Another aetiology that has been postulated is a genetic deficiency of calcitonin or its receptor.<sup>18</sup>

It is also possible that in a patient with an already compromised bone density, the mechanical stresses of late pregnancy may contribute to fractures occurring at that time.

### Investigation

The diagnosis of pregnancy- and lactation-associated osteoporosis should be entertained in any patient who presents with severe backache during late pregnancy or lactation. Typically, X-ray imaging of the thoracic and lumbar spine demonstrates multiple biconcave fragility fractures, but fractures may also be present in the ribs, pelvis or hips. The diagnosis can be confirmed by central DXA, which usually demonstrates very low spinal bone density and low bone density at the hip. The use of MRI to diagnose fractures is preferable as in the majority of these cases, previous X-rays are not likely to be available to exclude prior fractures. MRI, with the use of short TI inversion recovery sequence and the ability to show oedema, allows the recency of the fractures to be determined. There are no other diagnostic criteria, but it is essential to eliminate other secondary causes of bone loss. Calcium homeostasis should be fully investigated, including assessment of dietary calcium intake and the serum 25-OH D level. Euthyroidism should be confirmed and primary hyperparathyroidism excluded. Bone loss that is secondary to malignancy is uncommon in pregnancy, but should be considered. It is advisable to carry out protein electrophoreses to exclude myeloma. Biochemical markers of bone turnover may be increased at the time of diagnosis and can be used to monitor the course of the disease potentially.

### Management

If secondary causes of osteoporosis have been found, they should be treated. Numerous drugs have been

used to manage patients with pregnancy- and lactation-associated osteoporosis. These include bisphosphonates,<sup>1,2,21</sup> teriparatide,<sup>22</sup> strontium ranelate,<sup>23</sup> calcitonin<sup>18</sup> and calcium and vitamin D.<sup>18</sup> O'Sullivan et al,<sup>2</sup> in their review of patients who were treated with bisphosphonates, advocated treatment with bisphosphonates as it led to a greater increase in bone density than would be expected with conservative management. However, Kovacs<sup>18</sup> highlighted that given the low numbers of reported cases and the lack of control data, the efficacy of any specific treatment could not be assessed. As the majority of patients resolve spontaneously with conservative management, he suggested that intervention was not warranted, other than in desperate situations. Conservative measures include the cessation of breastfeeding and providing relief for the severe pain that is associated with fractures. As no comparative data are available, no firm conclusion can be reached as to whether or not active or conservative measures represent the treatment of choice. However, based on the limited available case reports, in the case of the patient who has developed vertebral fractures and who is of a young age, best clinical practice would be to treat her for one to two years with agents that are known to have short-term bone retention, such as risedronate, strontium ranelate or denosumab, rather than agents with long-term bone retention, such as alendronate or zoledronic acid.

#### Other conditions associated with bone loss in pregnancy

During pregnancy and the puerperium, heparin is commonly used as prophylaxis in patients who are at risk of venous thrombosis and in women with a history of poor obstetric outcome and recurrent foetal loss because of thrombophilia. The long-term use of unfractionated heparin in pregnancy has been associated with a 2.2-5% incidence of heparin-induced osteoporotic fracture, but data are scarce for low-molecular-weight heparin. Also, there is lack of clarity on the risk of osteoporosis and osteoporotic fractures.<sup>24</sup>

Transient osteoporosis of the hip is a distinct entity. It is a rare condition. Only 200 cases have been reported in men and women. It can occur in pregnancy or early postpartum and presents as pain in the hip or a limp. Usually, it is self-limiting and responds to conservative measures and bed rest. Resolution of symptoms and radiological changes occurs within a few months.<sup>18</sup>

#### Conclusion

Pregnancy- and lactation-associated osteoporosis is a rare cause of spontaneous vertebral fragility fractures. The presented cases support the body of evidence

that confirms the severity of this condition and the importance of having a high index of suspicion in patients who present with back pain in pregnancy and during lactation.

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