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Mini Review

An update on the mechanism and therapeutic implications of, pregnancy and lactation-associated osteoporosis; a narrative review

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Abstract

Pregnancy and lactation-associated osteoporosis is a rare form of osteoporosis that occurs during last trimester of pregnancy and lactation, causing bone resorption. This leads to bone fractures especially in the spine and hip. Symptoms are severe low back pain and physical disability and height loss. Pregnancy and lactation–associated osteoporosis occurs in three main forms: Post pregnancy spinal osteoporosis, transient osteoporosis of the hip, heparin induced osteoporosis in pregnancy. The aim of this article is to review the forms of pregnancy and lactation-associated osteoporosis.

Keywords: Pregnancy, Lactation, Osteoporosis

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Introduction

Suboptimal vitamin D is one of the preventable problems in the current century (1, 2). Pregnant women are at higher risk of suboptimal vitamin D level. Recent studies have reported the multiple effects of vitamin D on maternal, fetal, and child health. Among the classic effects of this vitamin we may note calcium homeostasis and bone metabolism (3, 4). In adulthood, in the absence of vitamin D [1.25 (OH) 2D] body cannot obtain the required levels of calcium and phosphorus (5).

In pregnancy, calcium is needed to grow and develop the fetus. The human embryo needs 21-30 grams of calcium until the end of pregnancy. About 80% of the mentioned amount of calcium accumulates in the third trimester, which actually requires the transfer of about 200-250 mg of calcium per day. Calcium actively passes through the fetus. Probably the active transfer site of calcium is located in the syncytiotrophoblast cell membrane. The fetal-placental unit acts almost independently from the mother's body system and the fetus's blood calcium level is higher than mother's blood calcium level (6). The increase in intestinal calcium absorption in the body of mother starts from the first trimester of pregnancy and doubles by the end of pregnancy. On the other hand, calcium excretion through urine increases during the time of pregnancy (7,8). During breastfeeding, the mother's body needs calcium even more than the time of pregnancy. Approximately, 300 mg of calcium per day is required to replace the calcium secreted in milk. During lactation, the level of intestinal calcium absorption reaches the pre-pregnancy level and the elevated urinary excretion of calcium decreases as well; however, because of the high prolactin level, low estrogen level, and the increase in PTH-related peptides secreted from the breast tissue, in order to provide the calcium secreted in milk, bone calcium absorption increases. This process results in rapid bone loss, especially in trabecular bones. It is estimated that about 5%-14% of bone mass is affected by this reduction process. In the first 6 months of weaning, bone mass returns to normal levels with a speed of 0.5%-2% per month (9).

Pregnancy and lactation-associated osteoporosis is a rare syndrome that occurs in form of unprompted fractures that is more common in spine body fractures and sometimes in the pelvis. Most cases occur in the late stages of pregnancy and early stages of postpartum and breastfeeding. It is transient and resolves after a few months. The main complaints of patients are extreme back pain, pelvic pain, and sometimes a decrease in height. Since the back pain is often attributed to the stiffness and toughness of the ligaments caused by pregnancy hormones, this complication may not be diagnosed. This condition is more common in women who experience their first time

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Implication for health policy/practice/research/medical education

Pregnancy and lactation-associated osteoporosis is a rare form of osteoporosis that occurs during last trimester of pregnancy and lactation, causing bone resorption.

of pregnancy, however, it might also occur in a minority of women who have experienced uncomplicated pregnancies in the past. Early diagnosis and treatment are necessary because fractures can be associated with severe morbidity. Pregnancy and lactation-associated osteoporosis occurs in three main forms (10).

Post-pregnancy spinal osteoporosis

Osteoporosis is commonly observed in women after the onset of menopause and also in aging women, but this form of osteoporosis is a potentially threatening disorder characterized by its low back pain in the late stages of pregnancy or after delivery. Decreased height due to compression fracture can also be associated with this type of osteoporosis (11).

The symptoms of compression fracture due to mild hit often occur, on average, a month after delivery. In such a condition, fractures are numerous and there is at least one known risk factor for osteoporosis, such as low bone density, smoking, familial history of osteoporosis/fracture, and vitamin D deficiency (12).

The increase in bone absorption occurs during pregnancy and lactation; sometime, due to decreased bone quality, it may also occur before pregnancy. PTH-related peptides that increase during pregnancy and lactation are a factor involved in increasing bone absorption. The increase in the excretion of calcium in the urine during pregnancy and the increase in prolactin and decrease in estradiol items during lactation are also among the factors involved in bone loss. Moreover, among the various factors, the role of genetics should not be ignored. As an example, we may note the genetic defect of calcitonin or its receptor. It is known that, in most cases the reduction in bone mass is resolved after pregnancy; it supports the hypothesis that the loss of bone mass is one of complication among a series of changes which occur ducting pregnancy and lead to increased bone absorption (9). By contrast, there are some factors protecting women against osteoporosis during pregnancy, including the increase in progesterone, weight gain, and adequate calcium intake, all of which help to improve bone density. In addition, the effect of the number of pregnancies and the duration of breastfeeding on osteoporosis in premenopausal women have been investigated in several studies, and their results have been contradictory (13-15).

The patients who develop severe back pain in the late pregnancy or lactation must be examined for the symptoms of osteoporosis during pregnancy and lactation. The diagnostic methods that can be used in such cases include the followings:

- *X-ray (plain radiograph):* Normally, the radiograph shows the lumbar and back segments and fractures with concavity on both sides. Although the fracture may also be seen on the ribs and pelvis.
- *Dual-energy X-ray absorptiometry (DXA, formerly DEXA):* It provides information on bone density and bone strength in the vertebrae and pelvis. When the results are significantly lower than the expected level, osteoporosis is confirmed. Its level is very low, but usually the test is avoided during pregnancy and if necessary it is postponed to a time after the delivery.
- *Magnetic resonance imaging (MRI):* It is used to test soft tissue, such as the disc between the vertebrae. It is also a method preferred for the diagnosis of fractures during pregnancy, because in most cases the results of previous radiographs are not available. Given the qualifications of STIR (short T1 inversion recovery) pattern of MRI, it can determine the newness of the fracture.
- *Radioisotope scan:* It can display hot spots in the site of fracture. However, it is not usually used during pregnancy and lactation.

There are no other diagnostic criteria, but it is necessary to discard the presence of other likely factors contributing to the decrease in bone density (secondary causes). Calcium homeostasis should be also investigated, for instance it is necessary to assess dietary calcium intake, the level of 25-hydroxy vitamin D, and thyroid and parathyroid function to ensure hypothyroidism status and discard the primary hyperthyroidism. The secondary reduction of bone density due to malignancy is uncommon in pregnancy, but it should be taken into consideration. It is also recommended to carry out protein electrophoresis to discard myeloma. In addition, biochemical markers of bone turnover increase at the time of diagnosis, which are potentially used to monitor the trend of the disease (9).

When secondary causes are identified, in addition to treating osteoporosis, these factors should also be treated. In other cases of pregnancy and lactation-associated osteoporosis, treatment methods are classified into two general categories: conservative treatment and treatment using osteoporosis-specific drugs.

Conservative treatments for the cases of fractures include the discontinuation of breastfeeding and the relief of severe pain in fractures (as they usually have the greatest level of pain during the first 6 weeks). In the event of severe pain, the patients are mainly recommended to take rest; however, long rest causes other complications, such as DVT and muscle weakness. Thus, the pain should be relieved sufficiently. Several methods are used to relieve pain, including the use of calcitonin, hydrotherapy, transcutaneous electrical nerve stimulation (TENS or TNS), alternative therapies such as acupuncture, heat therapy using hot pad, and cold therapy using ice pack.

The use of corsets for healing the fracture of the vertebrae is not recommended, except for a short time to relieve pain, because its long-term use may increase muscle weakness and discomfort. Other ways used to soothe and relieve muscle spasms after fracture include: proper respiratory habits, relaxation, ensuring adequate calcium and vitamin D intake, and exercise. Lumbar extensor strengthening exercises are beneficial, but lumbar flexion exercise should be avoided because it increases the risk of fracture of the vertebrae. There are controversial results about the positive effects of weaning and calcium and vitamin D supplementation for healing and recovering the loss of bone density.

Concerning special treatment, several medications are used for patients with this problem. These drugs include bisphosphonate, teriparatide, strontium calcitonin, vitamin k2, calcium, and vitamin D (9,16-19). But the best treatment is unknown. Among these drugs, the increasing use of bisphosphonates in women of childbearing age has focused attention on possible teratogenic effects of the drug. Bisphosphonates exit the blood after rapid absorption, but some of them (on average 68%), for years, remain in the blood as pharmacologically inactive sediments. They can enter the bloodstream again and have the ability to pass the placenta, thus when administering this drug for women of childbearing age, it is necessary to be cautious because long-term effects of the drug on the development of the fetal skeleton are not fully known. Animal studies have shown that the administration of very high doses of etidronate during pregnancy impairs the growth of the embryo's skeletal system, with a negative effect hundreds of times more than that of maximum human dose (10). Recently, a study has been conducted on 21 people to investigate the use of several types of bisphosphonates at pre-pregnancy or in the first trimester of pregnancy. In this study, bisphosphonates not only had no significant risk to the fetus but did not have side effects for the baby (20). Moreover, several other studies have shown that treatment with bisphosphonates does not affect the development and growth of fetus' bone (21,22).

Due to the lack of controlled and comparable results, it is not possible to make a definite conclusion and determine the best group of therapies for the patients. However, according to the limited available reports, for patients with vertebral fracture, the one- to two-year administration of drugs with short term bone reaction properties (such as risedronate, strontium, or denosumab) is preferred over the use of medications with long term bone reaction properties (e.g., alendronate and zoledronic acid) (9).

Transient osteoporosis of the hip (TOH) in pregnancy

This form is a non-prevalent and self-limiting condition with a complete recovery within 3 to 12 months. Middle-aged women are more at risk. It often occurs with limitation of pelvic girdle in the third trimester of pregnancy and may resemble different clinical conditions; moreover, it is associated with reduced bone density of the pelvis in radiography.

Most of the time, the left and right hip are involved with the same frequency (23). When a pelvis is affected, the opposite side is also involved in 30% of cases (24). Bone marrow edema or bone marrow reaction seems to be the background pathological condition. Radiographic changes may resemble the infection, osteonecrosis, or infiltrative neoplasm. In radiography, osteopenia is typically observed in the femoral head (if sufficient progress is made). Bone scan shows local increase in absorption in the femoral head. While in avascular necrosis (AVN), there is a reduction in central absorption. MRI shows the disseminated abnormality in bone marrow, that usually extends from the subchondral region of the femoral head to the intertrochanteric and subtrochanteric femoral regions. In such a condition, there is a reduction inT1signal and an increase in T2 signal. Changes observed in the MRI reflect the presence of edema or bone marrow reactions. But, unlike oscillatory necrosis, femoral head does not appear to be enlarged.

The reason for this condition is not clear, but there are some theories to explain it. These theories attribute it to the role of neurological factors, chemical agents, hormones, changes in blood flow due to pregnancy, ischemia, viral infection, and immobility. Embryo pressure on the urethral and sympathetic reflex dystrophy is also introduced as a neurological factor that causes of this condition. Hyperlipoproteinemia type 4 and electromyographic disorders have also been reported as cirrhosis comorbidity. The similarity between the transient pelvic osteoporosis and osteoporosis in other bony areas suggests a common cause for them; this complication is a syndrome associated with an increase in bone turn secondary to an unknown stimulus, which activates several nodes in the active femoral head, resulting in a large absorption of bone by osteoclasts. In later stages, they are replaced with osteoid and mineralization and remodeling occur. The reduction in bone density occurs from the time of bone absorption to the time of bone formation. At this stage, the bone is weak and prone to micro fracture. Restoration of these fractures leads to a periosteal reaction along the femur neck, and if the repair is inadequate, stress fracture occurs.

Pregnancy creates a unique physiological condition that is associated with major changes in calcium homeostasis in the mother's body; during pregnancy, the fetus has a considerable demand for maternal calcium deposits. Animal studies have shown a reduction in bone formation until the end of pregnancy (25). This condition continues after delivery and has a direct relationship with the duration of lactation. The hyperestrogenism condition during pregnancy protects mother's skeletal system against the demand for fetal calcium, while during the relatively short period of hypoestrogenism during lactation, baby's demand for calcium is provided by the movement of calcium from the skeleton of the mother. This process will

reduce bone density early in the postpartum period. The recovery of bone density occurs to the base level occurs up to about 10 months later. A study on humans has shown that bone density loss in the pelvis and lumbar spine was observed after six months of continuous breastfeeding. In addition, the increase in bone turnover during pregnancy is associated with the loss of bone mass, despite the presence of hyperestrogenism condition. During the postnatal period, the duration and severity of lactation are associated with a reduction in bone density. So women who had an experience of six months of continuous lactations more significantly suffered from a higher level of bone mass loss, as compared to those with shorter period of lactation (26).

Due to the non-specificity of the signs and symptoms in patients with transient pelvic osteoporosis, other possible causes of pelvic pain should be discarded. Therefore, it is necessary to collect data on the history of injury to the joint and discard many other lesions such as tuberculosis, avascular necrosis, malignant lesions, synovial chondromatosis, villonodular synovitis, osteoid osteoma, osteomyelitis, cholecysteine tuberculosis, infectious arthritis, and rheumatoid disease in the patient. Additionally, hyperthyroidism or excessive thyroxine replacement in a patient with hypothyroidism should be ruled out. In general, a good general condition and a benign nature of the lesion in terms of TOH and its high diagnostic suspicion, along with the clinical, laboratory, and radiological symptoms of the differential diagnosis described above, can help to achieve the correct diagnosis. Simple radiography may possibly not detect the condition and show localized bone mass until the disease is not fully developed, in such a condition MRI or bone scan may be necessary to confirm the diagnosis and rule out other causes. If delivery is not yet completed, the use of imaging techniques may be postponed until the late stages of pregnancy or after delivery (26, 27).

Many authors believe that none of the natural drug regimens can change the benign and natural trend of the disease and there is no need for treatment, except for conservative treatments and the adequate calcium and vitamin D supplementation, because this condition typically improves within 6-12 months. However, other treatment methods for this group of patients have been suggested, including non-steroidal anti-inflammatory drugs, bisphosphonates, bed rest, stretching, physiotherapy, sympathetic block, protected weighting, and calcitonin. In addition, deflazacort (a type of corticosteroid) is also used. In the case of calcitonin, although its direct effect on recovery cannot be proven, it is likely to accelerate the clinical recovery. It has also been shown that it has significant analgesic effects (through central or peripheral routes). This helps to mobilize the bone early and thus minimize the loss of bone mass that can occur over long periods of rest (26).

Heparin-induced osteoporosis in pregnancy

Heparin is used during pregnancy to prevent problems in patients at risk for frequent abortion or deep vein thrombosis (DVT). Long-term use of heparin (unfractionated type) is associated with a 2.2% to 5% increase in heparin-induced osteoporotic fracture (6). The data on low-molecular-weight heparin (LMWH) is less available (22).

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Conflicts of interest

The authors declare that they do not have any conflict of interest.

Authors' contribution

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