

Osteoporosis associated with Pregnancy

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Abstract

Osteoporosis has been recognized as one of the major diseases affecting individuals globally, including pregnant women and women who lactate. An enormous amount of calcium and other minerals are required for nourishment during pregnancy and lactation. During these critical stages, the homeostasis between osteoblasts and osteoclasts is perturbed. A higher serum level of calcium and minerals are needed due to a decrease in Bone Mass Density (BMD). Due to the decrease in bone mass, these people have a greater chance of acquiring osteoporosis and correspondingly any osteoporosis-related fractures. This review focuses on the physiology of bone and the development of osteoporosis during pregnancy and lactation.

Keywords: Bone mass density, lactation, nutrition, osteoporosis, pregnancy

Introduction

Although osteoporosis is considered a rare complication of pregnancy and lactation, it ranks among the three most common diseases affecting women in the United States, besides breast cancer and cardiovascular disease [1-3]. This disease affects approximately ten percent of the female population. Around 500,000 vertebral fractures [4] and 247,000 hip fractures [5] are reported annually. Hip fracture is considered the most serious osteoporosis-associated complication. Health care costs to treat this complication range from seven to ten billion US dollars annually [6]. This review focuses on the prevalence of osteoporosis associated with pregnancy, which occurs in pregnant women in the last trimester or shortly after delivery [7-9].

Anatomy and Physiology

The skeletal system, which consists of 206 bones, supports and maintains the framework of the body, aids in body movement, protects vital internal organs, acts as a mineral reservoir [10,11] and houses the bone marrow. Bone is a dynamic structure, composed of an organic framework embedded in an inorganic salt [10]. This organic framework is 80% cortical (compact) bone that provides rigidity and tensility and 20% trabecular (cancellous) bone that provide strength and elasticity [10-13].

The period of bone growth involves a continuous coupling process of bone resorption and formation, also known as the bone remodeling process [11,13-15]. Bone remodeling is a process initiated by the osteoclasts whose activity is regulated by several factors like PTH, glucocorticoids, vitamin D, sex steroids, insulin, prostaglandin and growth factors [16-21]. Cytokines, growth

substances, hormones, prostaglandins and nitric oxide also affect the bone remodeling cycle [22,23]. Endothelial cells are also reported to be involved in the bone's complex communication network with osteoblasts, osteoclasts, macrophages, stromal cells, and other cells present within the bone tissue [24].

Osteoblasts secrete osteoid, a bone matrix protein [11,13,16] and osteogenin [25], which initiate and promote osteogenesis. The newly formed matrix mineralizes in a span of 3 months, completing the bone formation process [11]. Through this process, people achieve maximum bone mass at the age of thirty-five [1]. After reaching maximum bone mass [5], the bone remodeling process becomes uncoupled, possibly due to impaired osteoblast function. Thus, especially for women who begin menopause, the rate of bone formation remains constant, but the rate of bone

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resorption increases due to the bone's increasing sensitivity to PTH [1]. This uncoupling process results in a net loss of bone mass density (BMD), which may lead to osteoporosis [4,15,23,24]. This pattern of bone loss is not uniform throughout the skeleton [4,25-29], but most commonly occurs at the vertebrae, proximal femur, and distal radius, which are highly trabecular in nature [4,27,29].

Pathogenesis

There are three types of diseases associated with bone. (A) Osteopenia is decrease in bone calcification or bone density. (B) Osteomalacia is a disease of adults that is characterized by softening of the bones. (C) Osteoporosis is a metabolic bone disease that reduces BMD, without any reorganization in its chemical composition, resulting in a high potentiality of bone fracture [1,30].

The two types of age-related osteoporosis are the postmenopausal (type I) and the senile (type II) osteoporosis [1,4,31,32]. Type I affects people within the ages of 51 to 75 years during the period of menopause. It is recognized as accelerated trabecular bone loss due to an insufficient level of estrogen present in the body. This increases the bone resorption rate leading to fractures of the vertebrae, distal radius and hip. Type II affects elderly people exceeding the age of 70 years with fractures of the hip and vertebrae [1,4,25,26,33]. Type II is characterized by nonaccelerated trabecular and cortical bone loss related to an insufficient level of vitamin D [1,4]. Estrogen deficiency is the most dominant factor in the pathogenesis of this disorder [34].

Osteoporosis induced softening of the bones usually occurs at the femoral necks, lumbar spine and other sites during the second or third trimester of pregnancy. The loss of BMD increases the possibility of bone fractures, which may seriously injure either the mother or child. Physiological adaptation to pregnancy under the control of complex hormonal regulating mechanisms prevents excessive resorption of calcium by the women's skeleton [35-37]. Thus the increase in maternal blood calcium in turn meets the demands of fetal requirement for calcium. Calcium deficiency may not be the only cause of transient osteoporosis. Several authors reported temporary failure of calcitrophic hormones and decreased activities of osteoblasts as other causes. Calcitrophic hormones and osteoblasts help the maternal skeleton adapt to the stress of childbirth [38,39]. Calcium homeostasis is affected by tocolytic therapy with magnesium sulfate [40,41]. Bone mass density declined in patients that were exposed to magnesium sulfate during the first to eleventh week postpartum [42]. Mothers with preeclampsia have reported paradoxical bone mineralization in twin-to-twin transfusion syndrome. Bone mineral content is reported to be higher in the osteopenic and polycythemic child than in the anemic and osteoporotic child [43]. However, by three months of age, the mineral homeostasis and biochemical levels return to normal [44].

PTH-related peptide (PTHrP) was recently identified as one possible factor that may contribute to the pathogenesis of pregnancy-associated osteoporosis [45]. PTHrP is produced during lactation [46] and is present in high concentrations in milk [47]. PTHrP concentrations are elevated during pregnancy, presumably contributing to a state of maternal

hyperparathyroidism (**Table 1**).

Osteoporosis could also occur with high doses of methotrexate and oral coagulants [48-50], through chronic estrogen deficiency associated with hypogonadotrophic hypgonadism, and through magnesium deficiency, which can be caused by chronic alcoholism [51,52]. Osteoporosis is associated with patients requiring large dosages of heparin [53,54]. Women, who have a history of thromboembolism, receive prophylactic antithrombotic therapy with heparin during pregnancy [55,56]. Heparin reduces BMD, causing osteoporosis or osteopenia [57,58,54-60]. Though it has been reported that, use of low-molecular-weight heparin instead of regular heparin, may avoid maternal osteoporosis [59]; further investigation is needed in this area. Ringe and Keller reported that the use of ossein-hydroxyapatite-compound (OHC), in conjunction with heparin, causes no significant change in bone mass [60].

Etiology

Hormonal, mechanical, and dietary factors are crucial to the maintenance of the skeleton, regulation of the bone remodeling process, and skeletal growth [26, 61,62]. Other supplementary factors involved in the development of osteoporosis are classified into demographic and genetic, reproductive status and history, dietary, environmental, behavioral, disease states, and drug therapeutic categories. The degree of osteoporosis varies in ethnic backgrounds due to differences in maximum bone mass, physical characteristics, and family history. West Indians and blacks have a lower frequency of osteoporosis than white Americans, northwestern Europeans and Asians [16]. Insufficient sunlight exposure and anorexia nervosa, which could be causes of vitamin D deficiency and malnutrition, may lead to osteoporosis [63,64]. Geographic area may also play an important role in the occurrence of this syndrome [6, 65].

Various lifestyles can also lead to osteoporosis. Sustained immobilization or a sedentary life-style may cause osteoporosis, by decreasing the activity of the osteoblasts resulting in an uncoupled bone remodeling process [6,10,26,66-68]. Environmental conditions like space flight may also affect the growth of the skeleton [69]. Astronauts experience loss of BMD in bones that carry weight and pressure under normal gravity [70]. Bone loss occurs in bones that carry weight under life-styles involving cigarette smoking, excessive alcohol consumption, and coffee drinking which inhibits the activity of the osteoblasts [5,25,26,68,71-73]. The development of osteoporosis may

(1)	Increase bone resorption of the maternal skeleton
(2)	Regulating cellular proliferation and differentiation
(3)	Development of the fetal cartilage and bone skeleton
(4)	Relaxing the vascular and nonvascular smooth muscle
(5)	Maintenance of reproduction system
(5)	Maternal-fetal calcium transfer
(6)	Parturition
(7)	Embryogenesis
(8)	Milk production

Table 1 Functions of parathyroid hormone-related peptide.

also be related to various medical conditions [74-78], diseases and pharmacological agents [4-6,79-85]. Breuil et.al., reported the first case of insufficient fracture of the sacrum revealing a pregnancy-associated osteoporosis. Medical conditions like hyperthyroidism, hyperparathyroidism, paralysis, chronic obstructive lung disease, intestinal malabsorption, renal dysfunction, malignancy, diabetes mellitus, pregnancy, and rheumatoid arthritis may cause osteoporosis. Pharmacological agents like corticosteroids, thyroid hormone, anticonvulsant, antacids containing aluminum, heparin, cancer chemotherapy, tetracycline, isoniazid and immunosuppressive agents, may lead to the development of osteoporosis (**Figure 1**).

Female Athletes in particular, have a tendency to develop osteoporosis, since they are under a lot of pressure to maintain a low percentage of body fat to achieve peak performance. Female athlete triad, which consists of disordered eating, amenorrhea, and osteoporosis becomes a common clinical entity amongst female athletes [86-91]. In addition, female athletes have decreased levels of sex hormones, together with other hormonal imbalances, such as sex steroid metabolism and menstrual irregularities, which lead to physiologic changes that result in bone loss [92-95].

Symptoms

Transient osteoporosis, also known as idiopathic osteoporosis, primarily affects the femoral neck of the hip and sometimes the lumbar spine and ribs [63,96,97]. Patients usually complain of a sudden onset of sharp pain following fracture or chronic backache [26]. Pain is generally felt in the periarticular, groin, buttock, upper anterior thigh, or hip pain during pregnancy [97-103]. However, pain in the hips can be mistaken for lower abdominal soreness [104,105]. Gunnar and Lindholm [100] stated four features that would represent a case of transient osteoporosis: "(a) Progressive hip pain that accentuates by weight bearing and develops shortly before or in the last trimester of pregnancy, (b) roentgenograms showing reduction of radiodensity of the femoral head and at times of the femoral neck and acetabulum, (c) excellent prognosis, thus pain subsides and the roentgenographic appearance returns

to normal within several months after delivery and (d) negative laboratory findings."

Diagnosis

Diagnosing osteoporosis during pregnancy is a challenging problem to the clinician as many of the available diagnostic procedures are recommended not to be performed on pregnant women. Osteoporosis patients are often recognized accidentally on X-rays taken for other purposes, such as fractures. On X-rays, radiolucency may indicate osteoporosis [13,27] of the appendicular skeleton, showing cortical thinning and the loss of trabecular bone, especially in the femoral neck. About thirty percent of the bone mineral content must be lost in order for it to appear on standard x-rays [13,104-106]. Vertebral fractures can be detected through x-rays, but radiographs are not an accurate method of detecting this syndrome **Table 2**.

Osteoporosis may be determined by examining one's BMD [6,107] by invasive or noninvasive procedures; invasive procedures include a bone biopsy taken from the iliac crest [6,70], which is the most accurate technique to identify osteoporosis [6]. A histomorphometry determines the degree of bone mineralization, the quantity and structure of the trabecular bone, the number of active bone cells, and the rates of bone formation and resorption. Noninvasive techniques include plain radiographs [6,13,70,77,106], radiogrammetry [6,106], single photon absorptiometry [70,106], dual photon absorptiometry [6,77,106], computed tomography [6,77,108-111], quantitative digital radiography [112], nuclear scanning of total body calcium and retention of Tc-labeled pyrophosphate. Without causing discomfort, these techniques provide accurate measurements of BMD. Reid et al. reported that total body fat is the best indicator of BMD in the skeleton [113].

Bone densitometry is the safest and easiest way of diagnosing existing osteoporosis [114]. Techniques used to diagnose low BMD are [1] the Quantitative Computed Tomography (QCT) of the spine, which images the vertebrae using low-dosage radiation and measures the mineral content [4] and the X-ray Absorptiometry (DXA) which images the spine and hip [115].

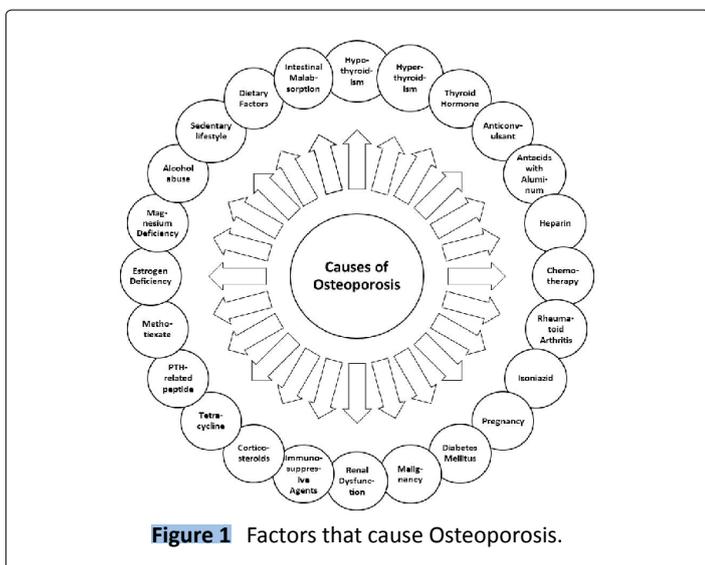


Figure 1 Factors that cause Osteoporosis.

Type of trace elements	Functions of trace elements
Aluminum	Inhibits osteoblasts causing hindering bone formation
Copper	Suppresses the functions of osteoclasts and osteoblasts, lowering bone turnover
Flouride	Increases bone mass by storing in new sites of bone formation
Gallium	Suppresses bone turnover in humoral hypercalcemia of malignancy
Iodine	Increases bone turnover when forming thyroxine and triiodothyronine
Magnesium	Stimulates osteoclastic cells to enhance bone turnover
Zinc	Influences bone turnover by secretion of calcitonin from the thyroid gland

Table 2 Trace elements involved in skeletal growth and development .

Lactation and Osteoporosis

Breast-feeding for three months in the United States is common with significant bone loss [63,102,116] followed by complete recovery of the cancellous bone, six months postpartum [56,63]. During this time, loss of BMD is reported to occur in the appendicular skeleton, particularly the trabecular bone [117]. Studies investigating longer periods of lactation have yielded different conclusions; they include lower bone mineral content at the lumbar spine [60,63], or radius [32,63] or no reduction in bone mass [52,63,96]. Lactation brings about physiological changes, which includes an increase in bone resorption and a rise in prolactin levels. Longitudinal studies revealed that periods of lactation greater than six months leads to significant bone loss at the lumbar spine (5.1%) [63,116], femoral neck (4.8%) [63,116], and distal forearm (7.0%) [46,63]. Nursing periods exceeding nine months have been associated with a significantly greater deficit in bone mass at one year as compared to women who nursed for only six to nine months [63,116]. Despite these documented bone losses, radial BMD seems to return to normal by as early as four months post weaning [46,63].

Osteoporosis has been shown to occur without the influence of lactation [40], but continuous lactation after the onset can further promote resorption [117,118]. In a nine-month time span, 400 mg/day of calcium is provided for the infant during lactation, which is four times greater than the amount of calcium lost in pregnancy [40].

Treatment

Once osteoporosis is diagnosed, appropriate treatments should be instituted immediately to control its development (Figure 2). Treatments include calcium supplementation, salmon calcitonin, estrogen, vitamin D, anabolic steroids, diphosphonates, fluoride, and coherence therapy. The use of calcium supplementation has positive effects towards achieving peak bone mass. Salmon calcitonin is used to prevent postmenopausal osteoporosis and to treat progressing osteoporosis [119]. Treatment with estrogen elevates the calcium balance and reduces bone loss. Estrogen Replacement Therapy (ERT) reduces the rate of bone turnover and inhibits bone resorption [116]. Other inhibitors of bone resorption are biophosphonates, which are consumed by the skeleton. Biophosphonates also increase bone formation and bone mineral content. Biophosphonates include etidronate and alendronate sodium [1, 120]. Stimulators of bone formation include sodium fluoride, calcitriol, PTH, growth hormone, growth factors (IGFs and TGF-beta), prostaglandin (PGE₂), strontium salts and anabolic steroids [1]. Though reported to be effective agents, none of the above-mentioned factors have been extensively studied, except for sodium fluoride. Magnesium therapy was reported to prevent fracture and increase bone mass density in patients with osteoporosis [46,121]. Some of the treatment modalities interfere with the normal development of the fetus and maintenance of pregnancy and hence the physicians should use extreme caution in the treatment aspect Table 3.

Osteosynthesis consists of repairing fractures by internal fixation with a mechanical device. In rare cases, osteosynthesis is used to help patients recover from bone fractures of the femoral neck,

and from osteoporosis in pregnancy [99,122]. Fractures of the femoral neck are diagnosed a few days before birth [123-125]. Hence, osteosynthesis is performed during the post-partum

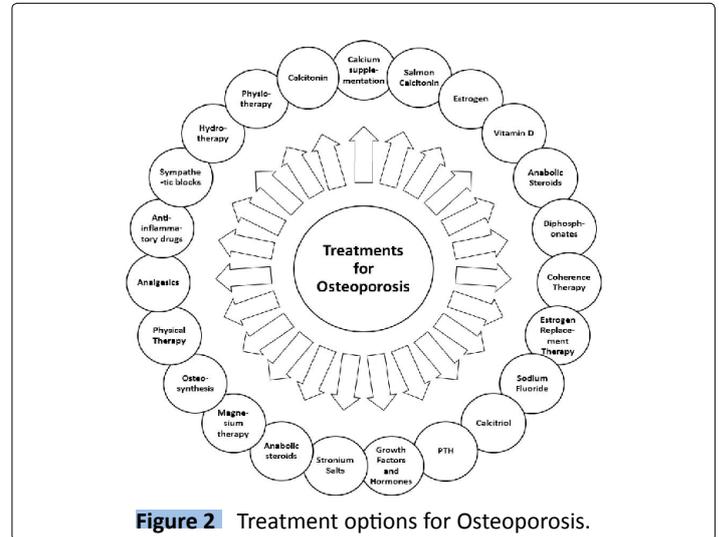


Figure 2 Treatment options for Osteoporosis.

	Osteoporosis of the Hip during Pregnancy (OHP)	Pregnancy Spinal Osteoporosis (PSO)
Effects	Bone mass density loss in the hips, spine and ribs; may lead to possible hip fractures	Bone mass density loss in the axial skeleton: the lumbar spine and proximal femur
Time of Onset	Late second or third trimester during pregnancy	Appears within three months after delivery of the first child
Symptoms	Pain to the periarticular, groin, buttock upper anterior thigh, and hips	Back pain, loss of height, and vertebral compression fracture
Diagnosis	Serum and urine content, radiogammetry, radiographs, single and dual absorptiometry, quantitative computed tomography and nuclear scanning	X-rays, serum and urine content, radiogammetry, radiographs, single and dual absorptiometry, quantitative computed tomography and nuclear scanning
Etiology	Deficiency of 1,25 (OH) 2D3, elevated levels of PTHrP, local ischemia, failure of calcitrophic hormones, high dosages of methotixate and oral coagulants, deficiency of estrogen, deficiency of calcium and magnesium, impaired venous flow, heparin therapy Magnesium sulfate and tocolytic agents	Cytokines: interleukin I (IL-1) Elevated levels of PTHrP
Treatment	Supplementation of calcium, estrogen, vitamin D, anabolic steroids, fluoride, diphosphonates, corticosteroids, calcitonin, Biophosphonates.	

Table 3 Differences between two types of osteoporosis associated with pregnancy.

period to reduce the risk of injury to the mother and infant [99].

Goldman et al. advised bed rest as the appropriate treatment for most cases without the need of any specific therapy [119]. Other therapies for transient osteoporosis include proper positioning of the patient, physical therapy to increase strength, analgesics, nonsteroidal anti-inflammatory drugs, oral or interarticular corticosteroids, sympathetic blocks, hydrotherapy, traction, physiotherapy and calcitonin to reduce bone resorption [100,101,126-131]. Remaining physically active, enhancing one's balance and coordination, and increasing muscular strength may reduce the occurrence of osteoporosis [132-134].

Discussion

During pregnancy and lactation, the fetus' physiological requirement of calcium burdens the maternal's calcium reservoir of the skeleton. The RDA intake of calcium for women is 1,200 mgs per day during these periods. During the third trimester, approximately thirty grams of calcium are needed for the fetal skeletal growth [135]. The National Institutes of Health Consensus reported that if the recommended levels of dietary calcium are met, there would be no loss in the mother's calcium level [135]. During lactation, women lose 160-300 mg of calcium per day in order to meet the infant's requirement for growth. Many women do not have enough calcium in their diet and are

undernourished. A deficiency of calcium propagates the mother's body to search for another source of calcium; one source is the maternal's skeleton. Losing the BMD in the mother's skeleton is recognized as osteoporosis associated with pregnancy.

Bones are largely composed of calcium [40]; more calcium is required during pregnancy and lactation because of "extra-cellular fluid volume expansion, increased renal filtration, placental transport to calcify the fetal bones and possibly, an increase in the maternal mass for the calcium demands of lactation" [40]. During the first trimester, the amount of calcium needed by the fetus is 2 to 3 mgs but increases to 250 mgs during the last trimester for skeletal growth. Deficiency of calcium causes the loss of BMD of the maternal's skeleton, through resorption, [98,136,137] leading to osteoporosis [58].

Despite the growing number of people suffering from osteoporosis or related fractures and the enormous financial support spent in managing osteoporosis, prevention of this disease has become the leading concern of health care systems worldwide. The health care systems are trying to detect the disease early to prevent further damaging. They are also limiting the number of disabilities, by providing rehabilitation [78] and moderate weight-bearing exercise programs, [68,118] for patients who are at a high risk or suffer from osteoporosis. The best way to prevent this syndrome is to increase awareness, to make a precise diagnosis,

and to institute prompt treatments and avoid invasive studies.

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