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Osteoporosis in Pregnant and Lactating Females: An Update

Gebe ve Emziren Kadınlarda Osteoporoz: Bir Güncelleme

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Abstract

The purpose of writing this review is to provide an update on recent advances in pregnancy and lactation-associated osteoporosis (PLO) research and summarize the current evidence for specific treatments. PLO is a transient and rare form of osteoporosis that affects women of childbearing age during the third trimester of pregnancy and post-partum. Though the pathophysiology of the PLO is poorly understood, several case series, case studies, and fewer cohort studies are available highlighting the role of pregnancy and lactation apart from conventional risk factors in the progression of PLO. Approximately 300 research and review articles related to PLO have been read from 1996 to 2023 which include several case studies, case series, cohort studies, meta-analyses, and narrative reviews from PubMed, Embase, Scopus, Google Scholar, World Health Organization regional databases. Common clinical manifestations include lower back and hip pain and rarely vertebral compression fractures. During pregnancy and lactation, women undergo reversible changes in mineral homeostasis and skeletal metabolism. Increased calcium absorption and urinary excretion during pregnancy and increased bone resorption along with renal calcium reabsorption in lactation are the main maternal metabolic adaptations that support the skeletal growth and development of the fetus and newborn respectively. Management of the PLO depends upon proper diagnosis and prognosis using biochemical bone turnover markers and bone histomorphometry. Conventional methods include calcium and vitamin D supplementation, giving up breastfeeding, physiotherapy, supportive braces, and bed rest. Bisphosphonates, denosumab, and teriparatide are commonly prescribed medications, assuring the recovery of bone mineral density besides certain side effects. Considering the transient nature, and underreporting of the cases, treatment recommendations should be personalized based on the parity, duration of lactation, presence or absence of fractures, societal status, age, ethnicity, and race.
Keywords: Osteoporosis, pregnancy, lactation, PTHrP, prolactin, teriparatide, bisphosphonates

Öz

Bu derlemenin yazılma amacı, gebelik ve laktasyonla ilişkili osteoporoz (PLO) araştırmalarındaki son gelişmeler hakkında bir güncelleme sağlamak ve spesifik tedaviler için mevcut kanıtları özetlemektir. PLO, gebeliğin üçüncü trimesterinde ve doğum sonrası dönemde doğurganlık çağındaki kadınları etkileyen geçici ve nadir bir osteoporoz şeklidir. PLO'nun patofizyolojisi tam olarak anlaşılamamış olsa da, PLO'nun ilerlemesinde geleneksel risk faktörlerinin yanı sıra gebelik ve laktasyonun rolünü vurgulayan birkaç olgu serisi, olgu çalışması ve daha az sayıda kohort çalışması mevcuttur. 1996-2023 yılları arasında PubMed, Embase, Scopus, Google Scholar, Dünya Sağlık Örgütü bölgesel veri tabanlarından gebelik ve laktasyonla ilişkili osteoporozla ilgili çeşitli olgu çalışmaları, olgu serileri, kohort çalışmaları, meta-analizler ve anlatı incelemelerini içeren yaklaşık 300 araştırma ve inceleme makalesi incelenmiştir. Yaygın klinik belirtiler arasında bel ve kalça ağrısı ve nadiren vertebral kompresyon kırıkları yer almaktadır. Hamilelik ve emzirme döneminde kadınlar mineral homeostazında ve iskelet metabolizmasında geri dönüşümlü değişikliklere maruz kalırlar. Gebelik sırasında artan kalsiyum emilimi ve idrarla atılımı ve laktasyonda renal kalsiyum geri emilimi ile birlikte artan kemik rezorpsiyonu, sırasıyla fetüsün ve yenidoğanın iskelet büyümesini ve gelişimini destekleyen ana maternal metabolik adaptasyonlardır. PLO'nun yönetimi, biyokimyasal kemik döngüsü belirteçleri ve kemik histomorfometrisi kullanılarak doğru tanı ve prognoza bağlıdır. Geleneksel yöntemler arasında kalsiyum ve D vitamini takviyesi, emzirmenin bırakılması, fizyoterapi, destekleyici breysler ve yatak istirahati yer almaktadır. Bisfosfonatlar, denosumab ve teriparatid yaygın olarak reçete edilen ilaçlardır ve bazı yan etkilerinin yanı sıra kemik mineral yoğunluğunun iyileşmesini sağlarlar. Olguların geçici doğası ve az bildirilmesi göz önünde bulundurularak, tedavi önerileri parite, laktasyon süresi, kırık varlığı veya yokluğu, toplumsal statü, yaş, etnik köken ve ırka göre kişiselleştirilmelidir.
Anahtar kelimeler: Osteoporoz, gebelik, laktasyon, PTHrP, prolaktin, teriparatid, bifosfonatlar

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Introduction

Osteoporosis is manifested by weakening of bone tissue, and disruption of bone microarchitecture leading to compromised bone strength, low bone mineral density (BMD), and an increase in fracture risk. It is estimated that there are more than 200 million osteoporosis affected people worldwide (1). Risk factors responsible for escalating the incidences of osteopenia and osteoporosis include pre-existing low BMD, aging, low calcium intake, smoking, low body mass index, estrogen deficiency, poor health, personal and family history of low trauma fractures due to osteoporosis, pregnancy and lactation (2,3).

Among all, conditions of osteopenia [T-score - between -1 and -2.50 standard deviation (SD)] and osteoporosis (T-score <-2.5 SD) are more prevalent in perimenopausal and postmenopausal women (4-6). The global prevalence of osteoporosis in women (perimenopausal and postmenopausal) is 23.1%, in premenopausal women between 2-4.7%, and in women below 40 years of age between 0.9-3% (7-9).

Pregnancy and lactation-associated osteoporosis (PLO) is a transient pathophysiological state characterized by back and hip pain, loss of height, lower BMD, and deteriorated bone micro-architecture. It is seldom presented with vertebral compression fractures. It is considered a rare form of osteoporosis however; the actual number of cases may be much higher due to less number of studies, poor awareness, and under-diagnosis. This may result in a poor prognosis of the disease (10,11). The PLO onset time is the third trimester of pregnancy to the early postpartum period during lactation (12). In the third trimester of pregnancy and during lactation, the skeleton experiences accelerated bone remodeling to meet growing calcium demands for fetal and neonatal skeletogenesis, apart from increased intestinal calcium absorption and urinary calcium excretion during pregnancy. This causes increased calcium release from the maternal skeleton leading to PLO (13).

In contrast to developed nations, the prevalence of PLO in developing countries could be more due to under-diagnosis, under-treatment, lack of awareness, multiparity along with prolonged lactation period, and malnutrition (11,14-16). The PLO can be more severe if the pre-pregnancy period has been with poor general nutrition including low calcium intake in the diet, low BMD along with positive family health history for osteoporosis (17). Though, bone loss associated with pregnancy and breastfeeding is transient and recovers fully at the same rate after weaning. However, in some cases, the skeletal calcium storehouse was depleted during lactation at the microstructural level and not fully replenished afterward (18,19).

Recent studies showed that frequent multiple pregnancies or multiparity and breastfeeding for longer duration is positively associated with vertebral fracture risks (14,20). In the case of multiparity, it has been observed that PLO with vertebral fractures may occur in any number of pregnancies (21). On the contrary, in one prospective cohort study which was carried out over 10 to 16 years of follow-up, parity and lactation each showed largely no correlation with the risk of osteoporotic fragility fractures, morphometric or morphological vertebral fractures, and changes in areal bone mineral density (22). Some studies also suggest that the patterns of parity and length of lactation have little or no impact on fracture risk or of pre- and post-menopausal women (23,24) instead length of lactation can provide protection against hip fracture in middle-aged and older women (25). One plausible explanation for this is that pregnancy and lactation may not be the risks for developing osteoporosis in long term.

A timely diagnosis of PLO and proper treatment can ensure a substantial recovery. To maintain skeletal homeostasis and normal during pregnancy and lactation, several preventive measures and management strategies can be suggested after reviewing biochemical and physiological parameters and BMD T-score. Some Food and Drug Administration (FDA)-approved drugs that are commonly prescribed are bisphosphonates, teriparatide, and denosumab. Currently, these drugs are prescribed along with calcium and vitamin D supplements for the management of osteoporosis in lactating females (26,27). The present review provides a holistic definition of PLO and discusses the likely mechanism involved in its onset, systematic investigations, and diagnostic tools with a brief discussion on the management of the disease. This present review is an effort to emphasize the significance of maintaining bone health in pregnant and lactating females and the need for carrying out epidemiological studies to arrive at conclusions necessary for setting up and/or updating guidelines.

Pathophysiology of PLO

In an adult, 99% of calcium is present in the bones as hydroxyapatite crystals [$Ca_{10}(PO_4)_6(OH)_2$] and the remaining 1% calcium is localized in the extracellular fluid and in the cell's cytoplasm either in ionized form or bound to albumin and in other chemical complexes (28). It is the ionized form that is physiologically relevant and is maintained in the narrow range of 4.65 to 5.25 mg/dL (1.16 to 1.31 mM). Calcium homeostasis is essential to life and is precisely regulated by the calciotropic action of four hormones: hypercalcemic factors -parathyroid hormone (PTH), parathyroid-hormone related peptide (PTHrP), and 1,25-dihydroxycholecalciferol (1,25-DHC popularly known as calcitriol) and the hypocalcemic factor calcitonin (CT). Calcium homeostasis is achieved by: 1) the absorption of the mineral by the small intestine; 2) bone formation and resorption, and 3) urinary and fecal excretion and renal reabsorption.

Mammals are viviparous, and have evolved costly postnatal care in terms of energy expenditure. Maternal physiology has developed a variety of reproductive adaptations. To fulfill the calcium requirement for the skeletal growth of the developing fetus and the newborn, maternal bone metabolism and mineral homeostasis comes into effect.

Bone is the major storage site for minerals and proteins in the body and is continuously renewed by a process called skeletal remodeling throughout one's life span. A bone remodeling cycle

involves the action of the osteoblasts or the bone-forming cells, which are responsible for the secretion of bone matrix proteins and bone mineralization; while osteoclasts are responsible for resorption by dissolving extracellular matrix and demineralization; whereas, post-mitotically converted osteoblasts or osteocytes send mechano-sensory signals (29).

At term, ~30 g of calcium gets accumulated in the skeleton of the newborn (13). About 80% of this accretion takes place during the third trimester at which time maximum fetal skeletal growth occurs. The maternal serum ionized calcium concentration remains unchanged throughout pregnancy. During pregnancy, intestinal calcium absorption gets doubled and urinary excretion is increased with a moderate increase in bone turnover (30). PTH level declines below normal in the first two trimesters and then rises to mid-normal in the third trimester in women with adequate calcium intake. CT, PTHrP, calcitriol, estradiol, progesterone, prolactin (PL), and placental lactogen all increase during pregnancy. All of these hormones directly or indirectly contribute to elevated maternal intestinal calcium absorption through active and passive pathways (31). *In vitro* and *in vivo* animal studies confirm that both PTH and PTHrP modulate the transplacental flux of calcium to the fetus and their production is regulated by calcium-sensing receptor (32,33). Under the condition of insufficient maternal intestinal calcium absorption, unable to fulfill the combined calcium requirements of the mother and fetus, the maternal skeleton experiences increased resorption during the third trimester (13).

After birth, neonatal mineral homeostasis becomes progressively efficient due to metabolic adaptations involving bone, intestine, kidneys, and liver (30,34). Generally, a lactating female transfers 200-300 mg of calcium/day from breast milk (35). During lactation, ionized calcium and total calcium remain normal to the non-pregnant values. Renal calcium reabsorption and to a larger extent calcium ion mobilization from the bone through increased resorption enhance calcium in the milk. The hormonal milieu is generally characterized by low estradiol and progesterone, increased PTHrP, PL, and oxytocin. PTH level falls to the lower end of the normal range, whereas calcitriol and CT fall within the normal range. These hormonal changes affect calcium metabolism and lead to changes in the bone remodeling process, eventually the rate of bone resorption increases (30,36,37). Bone resorption is independent of maternal calcium intake during lactation and causes a 5-10% loss of trabecular mineral content in order to deliver calcium to milk (31). Bone resorption mainly promotes the activation of osteoclasts and affects the BMD of breastfeeding women (38).

During lactation resorption of bone occurs mainly by two pathways:

(i) Upregulated Osteoclast-mediated Bone Resorption

In upregulated osteoclast-mediated bone resorption, serum levels of PTH and PTHrP have been reported to increase during lactation (39,40). Elevated PTH level promotes osteoclastogenesis followed by an increase in bone resorption, and serum calcium levels which in turn reduces bone mass (40).

(ii) Osteocytic Osteolysis

It is a phenomenon when osteocytes behave like osteoclasts to resorb minerals from bone matrix. Negative feedback by CT or a high-calcium diet can suppress osteocytic osteolysis. Low-calcium diet, and PTH are the positive modulators of this process during late pregnancy (41,42).

There is a "Brain-Breast-Bone-Circuit" which gets activated by suckling (39). PL hormone secreted by anterior pituitary lactotrophs causes a decrease in the levels of Gonadotropin-Releasing Hormone (GnRH) which leads to low circulating levels of follicle stimulating hormone, and luteinizing hormone and subsequently low concentrations of estrogen and progesterone (43). PTH level helps osteoblasts to increase the secretion of receptor activator of nuclear factor kappa B ligand (RANKL) and reduce the formation of an antiresorptive cytokine, osteoprotegerin (also known as osteoclastogenesis inhibitory factor) (44). PL is an important regulator of the bone remodeling process. It has mainly two receptor isoforms, namely prolactin receptors (PRLR) short and long, expressed in osteoblasts but not in osteoclasts. In an *in vitro* study, it was found that the PL hormone upregulated the expression of various osteoclastogenic modulators such as monocyte chemo-attractant protein-1, cyclooxygenase-2, tumor necrosis factor-alpha, interleukin-1 and ephrin-B1 which eventually lead to increased skeletal resorption during lactation (45). The accessory parathyroid gland in the breast produces abundant PTHrP which enters the maternal circulation, binds with its receptor present on osteoclasts, and accelerates the process of bone matrix resorption (36). Suckling activates the PTHrP expression and release (39). Thus, both PL and PTHrP are responsible for maternal skeletal calcium release (46). At the basolateral side of epithelial cells of mice mammary glands, PTHrP helps in the transcellular flux of calcium in milk (43). The calcium then reaches the neonatal circulation and gets immobilized along with collagen and other non-collagenous bone matrix proteins as a result of bone modeling.

Approximately, 6% loss in occurs during 6 months of exclusive breastfeeding, and this loss causes microarchitectural deterioration, though the bone loss is normally silent and does not lead to fragility fractures (10,36,47). Irrespective of the duration of lactation, the length of postpartum amenorrhea is an important determinant of bone loss (30). The rate of bone loss differs by skeletal sites (42), and the resorption rate is higher from the trabecular-rich spine and hip as compared to that of the appendicular skeleton (30,40).

Management of Pregnancy and Lactation Associated-osteoporosis

Biochemical Markers of Bone Turnover

Several changes have been observed in calcium metabolism and bone remodeling during pregnancy and lactation, and it is now important to understand the severity level of osteoporosis using several bone resorption and bone formation markers in serum and urine. These biochemical markers have been used

to gain a better understanding of the bone turnover dynamics during pregnancy and lactation (Table 1). Changes in the levels of PTH and 1,25-dihydroxyvitamin D do not play a role in reflecting the degree of bone loss during pregnancy (30,55) and during lactation (61). However, circulating level of calcitriol increases during the first trimester of pregnancy and influences the intestinal absorption of calcium (55). Serum concentrations of PTHrP increase during pregnancy which eventually results in bone resorption and increased urinary levels of pyridinoline and deoxypyridinoline significantly in the second and third trimesters (55). Increased levels of serum PTHrP and PL and decreased levels of estradiol are reported to be associated with lactation-induced bone loss during the first 6 months of exclusive breastfeeding (30). Increased bone resorption was studied by observing the increase in serum C telopeptide of type I collagen (CTX) which was twofold higher in lactating females than those of non-pregnant females, serum N-telopeptide of type I collagen (NTX) and urinary deoxypyridinoline also increases (13). Bone specific alkaline phosphatase and osteocalcin concentrations were higher in the lactating group than those in the control group (57).

During lactation, progressive loss of BMD can be assessed by dual-energy X-ray absorptiometry (DXA), and changes in bone histomorphometry can be assessed with the help of micro-computed tomography. High resolution-peripheral quantitative computed tomography is widely used for microarchitectural deterioration of bone tissue in breastfeeding females (Table 1) (58,62).

Prevention

Guidelines of various agencies worldwide (Table 2) recommend regular intake of calcium (1500 mg per day) through diet and/or with oral supplements during pregnancy and lactation. Similarly, for vitamin D, diet is sufficient but if deficiency occurs supplements of vitamin D (1000-2000 IU per day) can be recommended (68). In developed countries like the USA, there are several programs being run to fulfill the dietary need of pregnant and lactating females by considering the need of each socioeconomic group (64). In the developing world, where PLO is underestimated, under-diagnosed, and under-treated, such programs need to be developed and are necessary to run with proper assessment of socioeconomic status and needs of pregnant and lactating females. Assessment of biochemical bone turnover markers during pregnancy and after should be

Table 1. Biochemical and radiological bone turnover markers of pregnancy and lactation associated-osteoporosis

Phase	Bone turnover and histomorphometry	Vicissitudes	References
Pregnancy	Bone resorption markers	• Free pyridinoline and DPD (↑) • PTH (↓) • PTHrP (↑ in II and III trimester) • CTX (↑) • NTX (↑) • Calcitriol (↑ in I trimester)	(48-53)
	Bone formation markers	• BAP (↑) • P1NP (↑) • OCN (↓ in II trimester and ↑ in III trimester)	(49-53)
	Bone histomorphometry	• BMD (↓) • Tb. No. (↓) • Tb. Sp. (↑) • Tb. Th. (↓)	(48,49,54)
Lactation	Bone resorption markers	• Free pyridinoline and DPD (↑) • PTHrP (↑) • PL (↑) • NTX (↑) • CTX (↑) • Estradiol (↓)	(49,53,55,56)
	Bone formation markers	• BAP (↑) • P1NP (↑) • OCN (↔)	(49,53,55-57)
	Bone histomorphometry	• BMD (↓) • BV/TV (↓) • Tb. No. (↓) • Tb. Sp. (↑) • Tb. Th. (↑) • Cortical porosity (↑)	(49,58-60)

DPD: Deoxypyridinoline, CTX: Serum C-terminal cross-linked telopeptide of type I collagen, NTX: Serum cross-linked N-telopeptide of collagen I, PTHrP: Parathormone related peptide, PTH: Parathormone, BAP: Bone specific alkaline phosphatase, P1NP: Procollagen type I N-terminal propeptide, OCN: Osteocalcin, PL: Prolactin, BMD: Bone mineral density (g/cm^2), BV/TV: Bone volume fraction (%), Tb. No.: Trabecular number (mm^{-1}); Tb. Sp.: Trabecular separation (mm), Tb. Th.: Trabecular thickness (mm), cortical porosity (%)

Table 2. Recommendations for dietary calcium and vitamin D in pregnant and lactating females by different agencies

Serial number	Agency	Recommendations	Population	References
1.	CDC	Dietary recommendation of inclusion of low fat milk, cheese, yogurt etc.	American	(63,64)
2.	WHO	Dairy products for calcium in three portion of a day Vitamin D supplements in winter months and Northern Europe; Calcium supplements are available as tablets or capsules. Tablets (soluble tablets, effervescent tablets, chewable tablets for use in the mouth and modified-release tablets) are solid dosage forms containing one or more active ingredients.	For Europe and developing countries	(65,66)
3.	National Health Mission, Government of India	Swallowable tablets of 500 mg elemental calcium and 250 IU vitamin D3 in each tablet to be taken with meals two times a day.	Indian	(67)

CDC: Centre for Disease Control and Prevention, WHO: World Health Organization

carried out at regular time intervals. If required, DXA or pQCT can be recommended for BMD assessment postnatally. If the symptoms of osteoporosis appear, weaning off breastfeeding should be the first recommendation. However, it is important to mention here that all the above-mentioned guidelines are for general requirements of calcium and vitamin D during pregnancy and lactation and are not specific to PLO.

Therapeutic Interventions

The majority of case studies have reported that BMD recovers spontaneously after breastfeeding females have given up lactation within a year after weaning if no other causes are involved (69-71). On the other hand, secondary causes of PLO should be identified and treated. Some conservative strategies for the management of PLO include weaning off, calcium and vitamin D supplementation as per the above-mentioned guidelines (Table 2), avoiding lifting heavy weights, and physiotherapy (72,73). Patients with severe cases of osteoporosis (BMD T-score <-2.5 SD) or with vertebral compression fractures may be advised for using supporting vertebral corsets and bed rest to relieve back and hip pain (72,74). Along with weaning, certain medications can be given to treat these cases, though; no specific treatment guidelines have been developed for PLO as yet. PLO patients have commonly been treated either with anti-resorptive agents like bisphosphonates or anabolic agents like teriparatide depending on the severity of the case or the stage of the disease and sometimes these are used in combination or in a sequential manner (Table 3).

Bisphosphonates

Bisphosphonates are nitrogen-containing anti-resorptive compounds which show strong binding affinity to bone and are the most commonly used drugs. They inhibit the proliferation of osteoclasts, promote osteoclasts apoptosis, and modulate the bone turnover process so as to promote mineralization density (89). Commonly used bisphosphonates are alendronate, zoledronate and risedronate (49,90).

Therapeutic safety considerations of bisphosphonates treatment include complications of the upper gastrointestinal tract, fever, joint pain, transplacental transport, etc. (49,91,92). Data from animal and clinical studies suggest that they circulate in maternal serum, subsequently reach the placental barrier, and may have negative effects on pregnancy outcomes (early delivery, low birth weights, hypocalcaemia, and skeletal retardations of the newborns) (91,93). Generally, these drugs accumulate in the skeleton after their administration due to their high affinity with hydroxyapatite crystals (89,92).

Denosumab

Denosumab is a type of humanized monoclonal antibody which suppresses the RANKL-RANK signaling pathway of osteoclastogenesis. Denosumab binds to RANKL and prevents it from activating RANK thus helping in the suppression of bone resorption (94).

Accumulation of denosumab in breast milk has not been reported yet, but the drug can cross the placenta and affect fetal bone development (95). It can be used either alone or in combination with teriparatide as sequential therapy during lactation with satisfactory clinical efficacy (21).

Teriparatide

An osteoanabolic recombinant formulation, teriparatide shares similarities with the first 34 amino acids of PTH. Numerous case reports and cohort studies on the treatment with teriparatide of PLO patients belonging to different ethnicities and races are available (Table 3). It has been used to treat cases of PLO with a remarkable increase in the BMD at the lumbar spine, femoral neck, and hip with no new fracture and reduction in bone resorption markers (26,85,96-98).

This drug is commonly used due to its clinical efficacy and short half-life. However, the potential side effect is the risk of bone tumors, which is dependent on the dosage of teriparatide (21).

Table 3. Summary of some case reports, case series and cohort studies done in recent past including the important specifications related to the disease and treatment regimens

No. of cases (n) & age (yrs)	Period	Symptoms	Affected region	Tests
7 (30-39)	Pregnancy or lactation	Vertebral compression fractures or transient osteoporosis of the hip	T-score, lumbar spine =-3.2±1.0; left femur =-2.2±0.5; right femur =-1.9±0.5. Reduced trabecular and cortical thickness, no change in the trabecular number. Three novel mutations in LRP5, COL1A1, and COL1A2.	DXA (BMD), HR-pQCT, blood tests. DNA sequencing using MiSeq system
32 (31.3±2.6) (retrospective cohort study)	Third trimester/early postpartum	Vertebral fracture	Low lumbar spine BMD (Z-score =-2.5±0.7); femur neck (Z-score =-1.6±0.8) and total hip (Z-score =-1.5±0.8) BMD were less affected.	HR-pQCT, DXA, blood tests
107 (average 39.5) (Retrospective cohort study)	Third trimester/early postpartum	Vertebral fracture (at least one);	Most affected area are lumber and hip.	DXA
12 (31±5)	Pregnancy and lactation	Severe back pain, multiple vertebral compression fractures in 10 patients, 10 patients had vitamin D insufficiency	Mean BMD =0.894±0.153 g/cm^2 at lumbar spine, 0.728±0.090 g/cm^2 at femoral neck, and 0.728±0.080 g/cm^2 at total hip.	X-rays, DXA, blood tests for biochemical parameters
93 (18-40)	First month postpartum	Severe low back pain	Low BMD in relation to body mass index (BMI) in lumber, femoral neck and femoral overall.	DXA, blood tests (including level of vitamin D)
20 (33.9±4.6)	Postpartum	Vertebral fracture (5.4 fractures on an average) few have shown subsequent fractures in following years; Hip pain due to hip edema in a few, mental distress	Low BMD (lumbar spine T-score -3.3±0.9 and total femur T-score -2.3±1.0.	DXA, MRI, X-rays

Table 3. Continued

Treatments	Other specifications	Follow up duration	Region	References
Weaning, Ca and vitamin D supplements and teriparartide and denosumab.	Inclusion criteria-atraumatic or low traumatic cause, a temporal connection to the pregnancy and/or lactation. Skeletal risk factors-dental problems, drugs, endocrine disorders, historical height loss, immobility, previous fractures, (nutrition habits) as well as pregnancy and lactation.	–	Germany	(75)
27 patients were treated with teriparatide, Ca and vitamin D supplements; while 5 were treated only with Ca and vitamin supplements.	No evidence of secondary osteoporosis.	12 months	Korea	(26)
75.7% patients received bisphosphonates and/or parathyroid hormone derivatives (PTH) including vitamin D supplementation.	Included incident fracture cases and excluded patients with endocrine disorders known to affect bone metabolism such as osteogenesis imperfecta, osteomalacia, etc.	6 yrs	Germany	(47)
Alendronate or zoledronic acid.	Inclusion criteria: (1) occurrence of osteoporosis during terminal pregnancy or within 18 months post-delivery; (2) BMD Z-scores ≤-2.0; Exclusion criteria: (1) diagnosis of osteoporosis prior to pregnancy; (2) with other secondary osteoporosis.	24 months	China	(49)
Ca and vitamin D supplementation.	Exclusion criteria: (1) all individuals using antiresorbtive drugs, (2) taking vitamin D or calcium supplements, (3) with acute or chronic infections, (4) history of trauma or psychiatric disorders, (5) any secondary causes of inflammation.	6-12 months	Turkey	(76)
All patients received vitamin D (1000 IE/day). At baseline, 9 patients received teriparatide (for 2 yrs), 8 treated with bisphosphonates (for 5 yrs), 1 with denosumab, and 2 patients received no further medications. Two patients received teriparatide followed by 5 years of bisphosphonates treatment. All patients underwent a 3-week inpatient rehabilitation.	Excluded other causes of secondary osteoporosis.	2-16.3 yrs	Germany	(77)

Table 3. Continued

No. of cases (n) & age (yrs)	Period	Symptoms	Affected region	Tests
14 fracture subjects +79 non-fracture subjects (31-44)	Third trimester and early postpartum	Vertebral fractures	Low BMD (lumbar spine T-score -2.6 and femur neck T-score -2.0.	DXA, X-rays, biochemical examinations (urine and blood tests)
1 (24)	Postpartum	Severe back pain reduced vertebral height (T11-L5)	L1-4 T-score was -3.6 and femoral neck T-score was -3.1.	DXA, MRI, biochemical examinations
1 (35)	2 months postpartum (third pregnancy)	Back pain, multiple vertebral fragility fractures and height loss	Total lumbar Z-score -3.7, lumbar BMD =0.687 g/cm^2, total femur Z-score -1.5, total femur BMD =0.815 g/cm^2.	DXA, MRI, biochemical examinations
1 (33)	Early postpartum period	Severe back pain, multiple vertebral bodies with mild compression, especially in T12	The lumbar (L1-L4) BMD =0.602 g/cm^2 (Z-score =-4) and total hip BMD =0.741 g/cm^2 (Z-score =-1.6).	BMD, X-rays, MRI, CT, biochemical examinations
1 (33)	10 months postpartum	Low back pain and hip pain, left intertrochanteric fracture after falling from standing	L1-L4 (T-score is -2.8 to -3.5); hip neck (-2.7); hip trochanter (-2.2).	DXA, MRI, X-rays, biochemical tests
1 (36)	37 weeks of gestation 3 week postpartum diagnosis	Barton fracture at 37 weeks of gestation. Swelling and deformity of the wrist; restricted range of motion, lumber tenderness	Lumbar (L1-L4) BMD =0.714 g/cm^2 (Z-score =-2.9) and total hip BMD =0.717 g/cm^2 (Z-score =-1.7).	MRI, X-ray, DXA, biochemical examinations
42 (34.3±4.9)	Third trimester and postpartum lactation period	Vertebral compression fractures; transient osteoporosis of the hip or peripheral fractures	Z-score =-2.7±0.9 at the lumbar spine; pronounced reduction of trabecular and cortical thickness.	Genetic study, DXA, HR-pQCT, MRI biochemical examinations
27 (34.2±5.4)	Postpartum period	Severe back pain due to low energy vertebral fractures (VFs)	Low BMD of lumber and hip region (below -4.0) and trabecular region.	DXA, MRI, biochemical examination of bone turnover markers

Table 3. Continued

Treatments	Other specifications	Follow up duration	Region	References
Weaning, Ca and vitamin D supplement.	Study with fracture subjects started from postpartum visit while study with others started from pregnancy for before and after partum bone turnover markers.	-	Japan	(40)
Weaning, calcium and vitamin D and teriparatide 20 µg/day.	Anemia due to iron deficiency.	18 months	Iran	(78)
Weaning, calcium and vitamin D and teriparatide 20 µg/day.	No secondary cause of osteoporosis.	12 months	Turkey	(12)
Weaning, calcium carbonate 1200 mg/day, vitamin D3 650 IU/day, and alendronate 70 mg/week.	Never smoke or consumed alcohol. Followed a balanced diet during her pre-pregnancy and pregnancy. Neither experienced menstrual irregularities before pregnancy, nor pregnancy complications such as preeclampsia.	6 months	China	(79)
Weaning, calcium 600 mg/day, and vitamin D 1200 IU/day; underwent open reduction and internal fixation. Administered dalteparin sodium (0.2 mL/day, 2500 IU) to prevent deep vein thrombosis during the perioperative period and pain was alleviated with celecoxib (cyclooxygenase 2 inhibitor). Instructed to perform muscle strengthening exercises and moderately improve the range of motion in the hip and knee joints.	Breastfeeding at the time of presentation of fracture. Discontinued calcium and vitamin D after delivery.	–	China	(80)
Open reduction and internal fixation; weaning, calcium and vitamin D supplementation.	No family history of osteoporosis, and causes of secondary osteoporosis; no medical history of consuming alcohol, smoking, or using drugs. Discontinued taking calcium and vitamin D during pregnancy.	1 yr	China	(81)
Calcium and vitamin D supplementation recommended to all. Eleven patients with multiple vertebral compression fractures and a low bone turnover state treated with teriparatide (20 µg per day). Eighteen women received a bone-specific therapy 4 patients with the predominant occurrence of transient osteoporosis of the hip or a high turnover state treated with denosumab (60 mg every 6 months). Three patients treated with a combined approach (teriparatide + denosumab) due to severity (12, 5 and 6 vertebral compression fractures, respectively).	Loss of function mutations in LRP5 and WNT1 in 21 patients.	3 yrs	Germany	(56)
19 women received teriparatide (20 µg/day) (group A) plus calcium and vitamin D, 8 women with calcium and vitamin D only (group B)	Two cases identified with hyperthyroidism, one with anorexia nervosa, and one with inflammatory bowel disease. Nine had a positive family history of osteoporosis and nine received low molecular weight heparin during pregnancy.	2 yrs	Greece	(82)

Table 3. Continued

No. of cases (n) & age (yrs)	Period	Symptoms	Affected region	Tests
67 (31±2)	Postpartum period	Multiple vertebral fractures and lower back pain	Low spine and hip BMD.	DXA, X-rays, biochemical examinations
7 (30.6±3.3)	Pregnancy and postpartum	6 suffered vertebral fractures postpartum and 1 developed a hip fracture during the seventh month of gestation	Lumbar spine aBMD =0.772±0.115 g/cm^2, and Z-score =-3.2±0.7 SD. At the femoral neck, aBMD =0.683±0.133 g/cm^2 and Z-score =-2.0±0.9 SD. Low vBMD at distal radius.	HR-pQCT, DXA, biochemical examinations
1 (33)	Postpartum	Severe back pain, vertebral compression fracture	Low BMD (L1 & L4) femoral neck and total hip.	MRI, DXA, quantitative ultrasonometry (QUS) and an Xtreme-CT® (HR-pQCT)
47 (34.2±4.8)	Postpartum	Spinal fractures (mean: 4 fractures)	-	DXA, MRI, X-ray
9 (20-41)	Postpartum	Vertebral compression fractures (1 patient)	Four of nine cases were diagnosed with low bone mas; one case [accumulated doses of MgSO (4): 1,260 g] was diagnosed with PLO.	DXA
1 (29)	6 month pregnancy and 6 month postpartum	Severe back pain was located in the lower thoracic and lumbar regions since the sixth month of pregnancy	Kyphosis at L1 and L2 with mild scoliosis in the thoracolumbar region.	DXA, X-ray, MRI, biochemical tests
1 (47)	1 month postpartum	Severe low back pain, multiple vertebral fractures	Low bone marrow density (BMD) and a loss of height at the L1-L4 vertebrae.	DXA, MRI, biochemical tests
1 (34)	Pregnancy & postpartum	Leg pain during second trimester, severe hip and back pain during third trimester; multiple compression fracture postpartum	Multiple vertebral compression fractures (Th8 and Th12), height loss of all mid and low thoracic vertebra osteoporosis T-score lumbar spine =-4.2; total hip =-2.7.	DXA (aBMD), HR-pQCT, X-ray, MRI, biochemical tests; Genetic analysis (exome sequencing)

Table 3. Continued

Treatments	Other specifications	Follow up duration	Region	References
teriparatide (20 µg/day) with or without sequential antiresorptive therapy (ART).	Patients with osteogenesis imperfecta, osteomalacia, pre-existing osteoporosis, and secondary osteoporosis were excluded before PLO diagnosis.	3 yrs	Korea	(83)
-	At least one of the risk factors for osteoporosis (positive family history of osteoporosis, smoking, low calcium intake, hyperprolactinemia, kidney stones with hypercalciuria, treatment with high doses of glucocorticoids) was present.	-	Argentina	(48)
Denosumab was administered postpartum with 3000 IE vitamin D and 1000 mg of calcium daily.	No history of a secondary amenorrhea was found. The patient had always at normal weight/BMI. She had three abortions in the first trimester, an MTHFR polymorphism (C677C, heterozygous as well as a lipoprotein-a elevation) was found. A treatment with low-molecular heparin was initiated.	1.5 yrs	Germany	(84)
Subcutaneous injection of 20 µg teriparatide daily along with individually adapted vitamin D supplementation.	4 patients (7.8%) sustained a subsequent fracture, two after 3-5 months of treatment and two at >6 months of treatment.	2 yrs	Germany	(85)
-	Patients underwent long-term tocolysis with $MgSO_4$ (more than 8 days) for treatment of threatened preterm birth. (The accumulated doses of $MgSO_4$ were between 168 and 3,756 g). A positive smoking history (n=3). No family history of osteoporosis.	-	Japan	(86)
The patient was advised 2.5 mg of bromocriptine for the cessation of breastfeeding with 600 mg of calcium twice a week and vitamin D (6000 IU) once a week for 10 months. Bisphosphonate (alendronic acid) 70 mg pill weekly was advised as well.	History of miscarriage at four months of her pregnancy two years ago.	4 month	India	(87)
Romosozumab for 12-month, after 4 months of teriparatide injection.	Positive family history of osteoporosis; undergone a laparoscopic partial oophorectomy for the treatment of endometriosis.	1 yrs	Japan	(88)
Advised cessation of breastfeeding; calcium and vitamin D supplementation. Teriparatide 20 µg/day for 1 year followed by one dose of zoledronic acid (ZA).	No monogenic mutation; no secondary causes of osteoporosis.	7-40 months	Netherlands	(27)

aBMD: Areal bone mineral density, DXA: Dual-energy X-ray absorptiometry, HR-pQCT: High resolution-peripheral quantitative computed tomography

Other Anabolic Medications

Romosozumab and abaloparatide are two more FDA-approved anabolic interventions for the management of osteoporosis (99). Abaloparatide shares 76% homology to PTHrP and selectively activates PTHR1 favoring bone formation (100). Romosozumab is a monoclonal antibody that targets sclerostin secreted by osteocytes. The canonical Wnt/β-catenin pathway plays a crucial role in osteoblasts proliferation and differentiation. Sclerostin suppresses the canonical Wnt/β-catenin pathway by binding to low density lipoprotein receptor-related protein 5/6 (LRP5/6) co-receptors (101). Romosozumab binds to sclerostin and prevents inhibition of bone formation with mild adverse events (102).

Various clinical studies highlight the role of romosozumab and abaloparatide in improving BMD and bone turnover markers and a concomitant relief from back pain with no further fractures in postmenopausal osteoporosis (100,103,104). A 23.6% increase in lumbar spine, a 6.2% increase in femoral neck, and an 11.2% increase in total hip BMD of a 34-year-old woman who presented with severe low back pain and multiple vertebral fractures after she received romosozumab for 12 months has been reported (88). There were no reports on abaloparatide treatment of PLO women.

Kyphoplasty and Vertebroplasty

Kyphoplasty and vertebroplasty were reported for treating pregnancy and lactation-associated osteoporotic vertebral fragility fractures and compression fractures with other therapeutic interventions. Kyphoplasty and vertebroplasty are a very successful treatments for short-term pain relief for vertebral fractures (59,74,105,106).

Conclusion and Future Perspective

PLO is a rare disease and the number of cases is low, possibly due to underreporting and ignorance in the population about the situation mainly in the developing world. This calls for the need to reassess the societal status of the population while formulating new guidelines and public health policies. Further investigations into the correlation between pregnancy, lactation, and BMD, and subsequent risk of osteoporosis will provide new opportunities for early intervention, timely management, and prevention of PLO.

Treatment recommendations should be personalized based on number of parities, duration of lactation, presence or absence of fractures, societal status, age, ethnicity and race. By integrating the systems biology with P4 (predictive, preventive, personalized and participatory) medicine care social, psychological, economic and healthcare related burden can be reduced towards a more productive society.

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Ethics

Authorship Contributions

Concept: N.M., M.G., Design: N.M., M.G., Literature Search: N.M., H.M., M.G., Writing: N.M., H.M., M.G.

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