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NARRATIVE REVIEW

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Pregnancy- and lactation-associated osteoporosis: A position statement of the IAPM, IOF, ECTS, ESCEO, IMS, and EMAS

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Abstract

Pregnancy- and lactation-associated osteoporosis (PLO) is a syndrome characterized by fragility fractures (most commonly vertebral, often multiple) occurring in late pregnancy or the early postpartum period. This position statement summarizes the current knowledge of PLO, and the recommended procedure for assessment, diagnosis and treatment based on a review of published evidence. As PLO is a rare condition, controlled, comparative clinical studies are limited. Individual studies were reviewed, focusing on design, size, follow-up, evaluation of safety, and factors that impact PLO outcomes. Diagnosis of PLO should include a detailed clinical examination, a review of medical and treatment history, and laboratory tests to rule out secondary osteoporosis. Imaging techniques can be used to inform the appropriate treatment pathway, which will depend on whether the patient is antepartum or postpartum. Management of PLO and fractures includes calcium/vitamin D intake/supplementation, considering stopping breastfeeding, and analgesia, if necessary. Treatment with bone-specific agents should be evaluated on an individual basis to reduce subsequent fracture risk, noting that their use in PLO patients is off label. If pharmacological treatments are used, they must be given alongside effective contraceptive measures. Bisphosphonates can pass the placental barrier and are detectable in bone for years, so adverse effects on future pregnancies, although not yet reported, cannot be excluded. Preferred treatment options are teriparatide/abaloparatide or romosozumab. Second-choice treatments are denosumab followed by bisphosphonates or bisphosphonates alone. This position statement includes a pragmatic

Abbreviations: ECTS, European Calcified Tissue Society; EMAS, European Menopause and Andropause Society; ESCEO, European Society for Clinical and Economics Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; IAPM, International Academy of Perinatal Medicine; IMS, International Menopause Society; IOF, International Osteoporosis Foundation.

For affiliations refer to page 9.

approach for identifying women with PLO and suggests developing an individualized treatment plan that might include pharmaceutical intervention.

KEYWORDS
bone mineral density, fractures, lactation, pregnancy, pregnancy- and lactation-associated osteoporosis

1 | INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD) microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fractures.[1] The World Health Organization (WHO) defines the BMD threshold for osteoporosis as ≥2.5 standard deviations below the young adult mean peak bone mass when measured at the femoral neck and spine using dual-energy X-ray absorptiometry (DXA).[2]

Around 18.3% of the world's population is estimated to have osteoporosis with women having a higher prevalence (23.1%) than men (11.7%).[3,4] A systematic review and meta-analysis of population-based studies that used the WHO criteria for osteoporosis found an overall global prevalence of 19.7%.[5] The prevalence of osteoporosis is known to increase with age and is particularly high in postmenopausal women, with some reports estimating that around 50% of women over 50 years of age will suffer from osteoporotic fractures in their lifetime, twice the incidence seen in men of the same age.[6] The primary causes of morbidity, mortality, and healthcare costs due to osteoporosis are osteoporotic fractures, so the prompt identification and appropriate management of individuals at increased risk for fractures is critical.

In addition to low BMD, several other independent risk factors for osteoporosis have been identified.[1,5,7] These include age, gender, premature menopause, a family history of osteoporosis or hip fracture in a parent, low body weight, lifestyle factors (e.g., low intake of calcium and vitamin D, inactivity, smoking, and excessive alcohol intake), and certain medical conditions (e.g., diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, breast cancer, and chronic liver and kidney disease). In clinical practice, fracture risk assessment tools, including FRAX (developed by the Metabolic Bone Disease Unit at the University of Sheffield in 2008), which combine BMD measurements and assessment of a range of possible clinical risk factors, are commonly used to determine 10-year fracture risk in individuals over the age of 40 years[8,9]

From a clinical management perspective, it is important to differentiate between primary and secondary osteoporosis, a distinction that is dependent on their underlying causes. Primary osteoporosis is the most common form and includes idiopathic osteoporosis occurring in both women and men, usually as a result of natural aging or due to hormonal changes, for example low estrogen levels in postmenopausal women.[1] In primary osteoporosis, no other disease or external factor can be identified as the cause of bone loss. Secondary osteoporosis is less common, but well documented, and arises as a result of other medical conditions or due to treatment with medications that cause bone loss or hormonal changes. Examples include endocrine disorders (e.g., diabetes mellitus type I, hyperthyroidism, hyperparathyroidism, and premature ovarian insufficiency), chronic diseases such as rheumatoid arthritis or Parkinson's disease, long-term use of certain drugs (e.g., glucocorticoids, depot medroxyprogesterone acetate [DMPA], chemotherapy, aromatase inhibitors used to treat breast cancer in women, and heparin).[1,10,11] Other factors include malabsorption of calcium and vitamin D, anorexia nervosa, prolonged immobilization, and possibly advanced maternal age at first pregnancy.[12]

A rare form of osteoporosis, and the focus of this joint position statement, is pregnancy- and lactation-associated osteoporosis (PLO).[13–16] PLO can be defined as a clinical syndrome characterized by fragility fractures (most commonly vertebral, often multiple) occurring in late pregnancy or the early postpartum period, usually, but not always, accompanied by low BMD for age. As PLO can have a significant negative impact on bone health and substantially reduce long-term quality of life,[17] there is a need to raise awareness and recognition of PLO among all healthcare professionals who care for women through pregnancy and in the postpartum period to ensure prompt referral for specialist evaluation. Clear strategies are needed to assist clinicians with assessment and diagnosis of PLO and to direct appropriate treatment. This joint position statement, developed by several interdisciplinary obstetrics and bone societies, provides a review of the available literature regarding what we currently know about PLO and its management and proposes algorithms to help clinicians determine the most appropriate pathways for diagnosis and treatment of women in their care.

2 | PHYSIOLOGY OF NORMAL BONE TURNOVER

To provide important context to the discussion of PLO and its management, key drivers of the physiology of normal bone turnover in premenopausal women and the influence of estrogen and other hormones on bone health during pregnancy and lactation are briefly reviewed.

2.1 | Bone turnover in premenopausal women

During adolescence in girls, estrogen levels rise significantly and this change affects bone development as well as reproductive health.

The increase in estrogen levels triggers the onset of puberty and the start of menstruation. Throughout adolescence, estrogen levels continue to increase steadily, resulting in the acceleration of bone growth and the closure of epiphyseal growth plates.[18] This period is recognized as critical for achieving peak bone mass in adulthood. Estrogen levels eventually reach a steady state with the establishment of regular menstrual cycles and bone turnover becomes balanced, with consolidation of bone mineral density and architecture until adulthood. Typically, peak bone mass is achieved by the end of the second decade of life, but it varies by skeletal site, sex, and population, and while much of bone accrual occurs by late adolescence, peak or plateau BMD might not be reached until the third decade of life or later.[19–23]

2.2 | Influence of pregnancy on bone health

During pregnancy, estrogen levels increase significantly, produced primarily by the ovaries and placenta, and peak in the third trimester, to support the growth and development of the fetus and prepare the mother's body for childbirth and lactation.[24] To meet the requirement of the developing fetal skeleton during pregnancy and its growth postpartum, maternal metabolism undergoes some significant adaptations, particularly with respect to calcium homeostasis[25–27] (Figure 1).

During pregnancy, approximately 30 g of calcium is transferred from the maternal skeleton to the fetus, and most of this (around 80%) occurs during the third trimester.[28] To compensate for such requirement, and to support fetal bone accretion during pregnancy, a twofold increase in maternal fractional calcium absorption is observed, resulting from a twofold to fivefold increase in 1,25-dihydroxyvitamin D (calcitriol) levels derived from maternal kidneys.[25,29] Both estrogen and prolactin, which are elevated in the third trimester, promote calcium absorption indirectly by increasing the production of 1,25-dihydroxyvitamin D. This is balanced by an increase in urinary calcium excretion through the kidneys; however, renal conservation of calcium is also observed.[30,31] Other maternal compensatory mechanisms of calcium homeostasis and bone turnover during pregnancy include elevated estradiol (from the ovaries and placenta), which influences calcium absorption and bone metabolism,[28,30] PTH-rP, and osteoprotegerin (OPG) levels. OPG inhibits bone resorption by binding to receptor activator of nuclear factor kappa B (RANK) ligand (RANKL) and blocking the signaling pathway that regulates osteoclastogenesis and osteoclast activation and inhibiting excessive bone resorption.[32,33]

The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine recommend serum/plasma procollagen type I N-propeptide (P1NP) and serum β isomerized C-terminal telopeptide of type I collagen (β-CTX-I) as reference bone turnover markers for osteoporosis.[34] During pregnancy, particularly in the first two trimesters, the levels of these bone turnover markers are low to normal but increase rapidly in the third trimester.[35] Studies using DXA and quantitative ultrasound (QUS) have demonstrated relatively stable BMD levels in pregnant women during the first trimester with some decreases in the second trimester, but the most significant decreases are observed in the third trimester.[36–41] However, the degree of bone loss varies by location. For example, one study found a significant

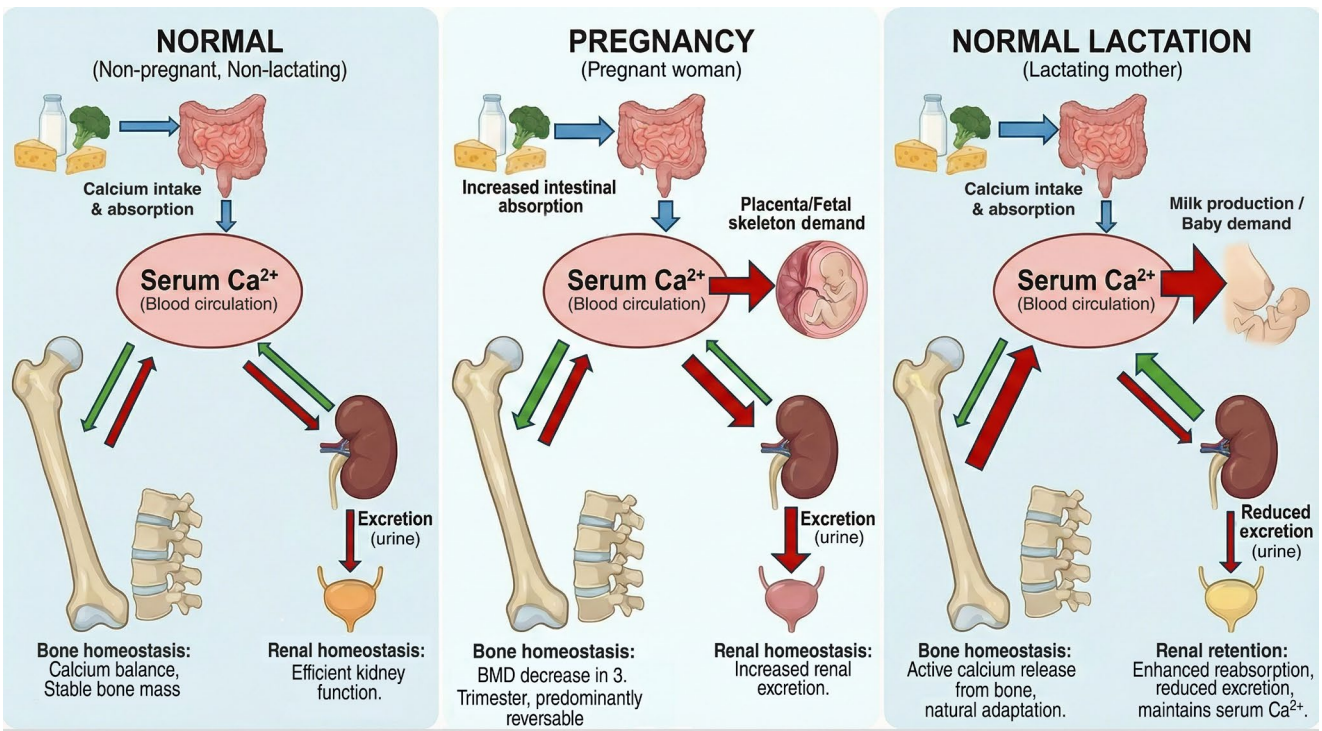

FIGURE 1 Pathophysiology of the calcium pathway in normal, pregnant and lactating women.

decrease in BMD at the ultra-distal radius (approximately 2%), spine (approximately 1.8%), and total hip (approximately 3.2%) and a larger decrease (4.2%) at the trochanteric region.[42] Breasail et al., using peripheral quantitative computed tomography (pQCT) and HR-pQCT scans of tibia and radius, found significantly greater decreases in total BMD, trabecular volumetric (v) BMD and cortical vBMD in pregnant versus non-pregnant women, as well as pregnancy-related decreases in bone microarchitecture.[43] Bone microarchitecture deterioration was observed in women with PLO, with the trabecular compartment being the most affected. It showed significantly lower trabecular density, number, and thickness, with subsequent greater trabecular separation and network heterogeneity. Concerning the cortical compartment, its density and thickness were also deteriorated but to a lesser extent. For most women, the changes in BMD are temporary, and it usually returns to its pre-pregnancy level after 1 year of weaning.[44–46]

2.3 | Influence of lactation on bone health

During lactation, estrogen levels decline rapidly due to rising levels of prolactin, which suppresses hypothalamic gonadotropin-releasing hormone.[47] This reduces the release of the pituitary gonadotropins, luteinizing hormone and follicle-stimulating hormone, thereby inhibiting ovarian estrogen production. The rising prolactin levels, as well as suckling, stimulate milk production and promote parathyroid hormone-related protein (PTHrP) secretion from mammary tissue. PTHrP acts synergistically with low estrogen to mobilize calcium from the maternal skeleton, contributing to bone loss during breastfeeding.[47] It is estimated that women lose 300 to 400 mg of calcium daily through breast milk, and this calcium demand is met by a 5–10% loss of skeletal mineral content during 6 months of exclusive lactation.[27,48] The hypoestrogenic state and the increased demand for calcium are key drivers of this increased bone resorption during lactation[49] (Figure 1). Calcitriol levels also remain high during the postpartum period, which can help offset skeletal calcium mobilization. Further, insufficient levels of vitamin D, due to factors such as lack of exposure to sunlight or poor dietary intake, can contribute to low calcium absorption and exacerbate bone loss during lactation.[50,51]

Bone turnover studies in both experimental animals and nursing women have largely also found that levels of bone resorption markers, such as collagen type 1 c-telopeptide (CTX) and n-telopeptide (NTX), are elevated during lactation.[47] Recent studies in animal models suggest that brain-derived cellular communication network factor 3 (CCN3) secreted from KISS1 neurons of the arcuate nucleus (ARC/KISS1) can act as a potent osteoanabolic factor that can build bone in females during lactation.[52] While these findings are interesting, translational clinical studies are needed to establish its role in lactating women.

In general, studies suggest that bone loss during lactation is transitory and usually there is a recovery of BMD at all sites studied, depending on the return of menstruation after weaning.[53] A meta-analysis of studies evaluating BMD during lactation found that the duration of lactation was also an important factor in outcomes: at 12 months postpartum, the group of women who breastfed for >6 months had significant losses at the lumbar spine, while those who breastfed for a shorter duration (≤4 months) had recovered their BMD at that timepoint.[54] Overall, however, accumulated evidence suggests that lactation does not have any long-term negative effects on the maternal skeleton[49,55,56] and does not translate into an increased risk of fragility fractures.[46,55,57,58]

Despite known compensatory mechanisms that help promote a restoration of bone after weaning, there is a subgroup of women who suffer from a severe form of PLO.[13,59,60] These women present with more severe bone microarchitecture impairment than control women undergoing a similar profound process of trabecular bone resorption during lactation, which is in line with the hypothesis that bone quality might in fact be deteriorating before gestation in most patients, and consequently they are unable to meet the increased calcium requirements.[61,62] It is worth noting that, although not always available, HR-pQCT is a useful noninvasive tool for assessing bone microarchitecture, offering new insights into the pathophysiology of PLO.[63]

3 | DEVELOPMENT OF THIS POSITION STATEMENT ON PREGNANCY- AND LACTATION-ASSOCIATED OSTEOPOROSIS

Searches were undertaken of PubMed and MEDLINE (National Library of Medicine, Bethesda, MD), as well as other databases, to identify clinical trials, systematic reviews, meta-analyses, narrative reviews, observational studies, case–control studies regarding PLO and its management up to 2025 with the following search terms: [pregnancy OR lactation] AND fracture, osteoporosis, BMD, QUS, high-resolution peripheral quantitative computed tomography (HR-pQCT), and bone turnover markers. In addition, the Cochrane Register of Controlled Trials and database of ongoing and unpublished trials were searched (www.clinicaltrials.gov). The retrieved literature, including primary studies, published reviews and case reports, was examined and interpreted in the context of existing consensus documents and clinical experience but were not assessed or graded for level of evidence. These findings were used to propose the most appropriate diagnostic methodology, determine the choice of therapy, and define follow-up/monitoring procedures.

Over the past decade, several reviews and meta-analyses[13–15,26,27,61,64–68] as well as retrospective cohort analyses[59,69,70] have provided helpful summaries of the available clinical evidence about PLO and best practice insights into its management. In developing this position statement, we have reviewed these previous publications alongside evaluation of recent data, individual clinical studies, and case reports to develop suggested algorithms for assessment, diagnosis, and treatment of PLO that can be used in routine clinical practice. PLO is a condition that requires an individualized approach to care and multidisciplinary team input, with the wellbeing of both the mother and unborn child taken into consideration.

4 | INCIDENCE, RISK FACTORS AND PATHOPHYSIOLOGY OF PREGNANCY- AND LACTATION-ASSOCIATED OSTEOPOROSIS

4.1 | Incidence

Pregnancy- and lactation-associated osteoporosis is a rare condition and, coupled with the fact that there is a lack of robust epidemiological studies in this setting, definitive figures for incidence and prevalence are difficult to establish.[59] A retrospective single-center study that evaluated medical records over a 20-year period estimated a PLO prevalence of 4.1 in every 100 000 women of reproductive age.[59] In addition, nationwide data from Japan suggest a rate of 4.5/10.000, but this included fractures occurring within 2 years of obstetric hospitalization.[71] A recent systematic literature review and meta-analysis aimed to estimate the prevalence of PLO in postpartum women within 1 year of delivery.[72] Eight observational studies were identified and seven of these used DXA to assess BMD. However, they used different parameters to assess osteoporosis (*T*-score, *Z*-score, or a combination of both) and different timeframes for evaluation, highlighting the challenge of comparing data across studies. With these limitations in mind, the estimated prevalence of PLO defined by DXA was 5% at the lumbar spine and 12% at the femoral neck.[72]

4.2 | Risk factors

Potential risk factors for PLO often overlap with those described earlier for idiopathic osteoporosis.[15] A large observational case–control study that directly compared 102 women with PLO and 102 healthy controls found that those with PLO had significantly more dental problems in childhood, were less physically active both before and after puberty, and were less mobile during pregnancy.[60] Other potential risk factors that have been reported include a family history of osteoporosis and osteoporotic fracture, the presence of conditions such as type 1 diabetes mellitus or rheumatoid arthritis, and a history of anorexia nervosa.[15,17,27,69,73] There is also an epidemiological relationship with ovulation disorders, a history of infertility treatment, and advanced maternal age.[12,72]

Medications that might contribute to osteoporosis risk in premenopausal women include thromboprophylactic agents such as low-molecular-weight heparin (which is widely used in pregnancy), corticosteroids, tamoxifen, aromatase inhibitors, anticonvulsants, DMPA, and luteinizing hormone-releasing hormone agonists.[59,64,72]

Other possible underlying causes for PLO include previously undiagnosed metabolic bone disease or monogenic forms of osteoporosis, such as osteogenesis imperfecta, and the presence of genetic mutations such as *COL1A1*, *COL1A2*, *RPDV*, *LRP5*, *Wnt1* and *LPR5/WINT1*.[15,74–80] If available, genetic testing should ideally be undertaken in women with suspected PLO, to determine if they have any previously unrecognized skeletal rare disorders.[78] In addition, as bones and teeth share some characteristics of development and mineralization, it has been suggested that the presence of dental disorders might be a potential marker for congenital rare bone conditions, with phenotypes often present in PLO.[81]

4.3 | Clinical presentation

Women subsequently diagnosed with PLO generally present with severe pain, most commonly back pain, often combined with height loss.[82] These symptoms occur predominantly in the last trimester of pregnancy and during lactation, mostly during the first pregnancy, rarely in the second or third. Many patients report multiple consultations before finally being correctly diagnosed with PLO, which might indicate a high rate of underdiagnosis and underscores the need to raise awareness of the condition and provide guidance for assessment and management. Vertebral fractures are the most common type of fracture observed in PLO and are generally the underlying cause of the low back pain and height loss.[82] Patients often present with multiple vertebral fractures with, one review reporting a mean of 2–5.8 vertebral fractures per patient.[66,83] Commonly, fractures occur in the thoracic and/or in the lumbar spine, indicating the need for evaluation of both if PLO is suspected. Non-vertebral fractures might occur but are less common; they can include those of the hip, femoral neck, sacrum, radius, humerus, ribs, and feet.[15,66] Some patients might experience hip pain accompanied by gait impairment, which might result in increasing immobility and/or fractures. In these patients, transient osteoporosis of the hip (TOH) should be considered as an alternative diagnosis. This is a recognized cause of hip fracture in pregnancy but is distinct from PLO and is characterized by localized edema visible on magnetic resonance imaging (MRI) and not skeletal resorption.[16,84–86] In TOH, pain is localized to the hip, often unilaterally, with no other skeletal sites involved, and it generally resolves spontaneously postpartum.

4.4 | Pathophysiology

Studies at the tissue level suggest that the characteristics of bone structure and metabolism seem to differ between women with PLO and those without PLO or with idiopathic premenopausal osteoporosis. In a case–control study, women with PLO were found to have a more severe clinical presentation (significantly more total fractures, more vertebral fractures, and higher prevalence of multiple fractures), with more profound BMD deficits and lower tissue-level rates of mineral apposition and bone formation[87] than the comparative cohorts. In addition, they had lower serum levels of the bone turnover markers P1NP and CTX than the cohort with idiopathic osteoporosis. In a retrospective single-center study, BMD assessments using DXA, bone microarchitecture analysis using HR-pQCT, and measurements of bone turnover marker in seven women with PLO found severe deterioration of bone trabecular and cortical microarchitecture compared with a control group of healthy lactating women.[62]

Data on the long-term outcomes of women with PLO are limited, but a single-center prospective cohort study that investigated subsequent fracture risk of 107 patients with PLO found that after 6 years of follow-up, almost 25% of these patients had sustained a subsequent fracture, and this fracture risk correlated with the number of fractures at time of PLO diagnosis.[88]

5 | RECOMMENDATIONS FOR ASSESSMENT AND DIAGNOSIS OF PREGNANCY- AND LACTATION-ASSOCIATED OSTEOPOROSIS

The proposed pathway for assessment and diagnosis of women with suspected PLO will differ depending on whether they are antepartum or postpartum (Figure 2). Women with severe and persistent back pain during pregnancy or lactation should be referred for further specialist diagnostic procedures. For all patients, initial assessment should include a detailed review of their family and medical history to evaluate osteoporosis-related risk factors, especially of secondary causes of osteoporosis. This should include discussion of any previous and current pharmacological treatments, plus a physical examination, including documentation of height for clinical signs of fracture.

Women with clinical signs of fracture, which might include a height loss of ≥3 cm, who are currently pregnant should be referred for MRI, but this should be performed without the use of contrast agents because they are contraindicated during pregnancy. If no fractures are present, conservative management is recommended, but if a recent peripheral or vertebral fragility fracture (Genant grade II) is observed, it is recommended that the patient's medical history and medical treatment are reviewed again to check for any oversight and a full laboratory work-up undertaken. Routine blood tests are needed to identify any possible secondary cause of osteoporosis. These should include C-reactive protein, complete blood count, calcium, phosphate, alkaline phosphatase, glucose, liver function tests, creatinine, thyroid-stimulating hormone, estrogen, 25-hydroxyvitamin D, parathyroid hormone, and protein electrophoresis. Additionally, the assessment of biochemical markers of bone turnover (CTX and P1NP) might be useful. This laboratory work-up should preferably be performed after delivery (post weaning) as some laboratory values will be affected by pregnancy. In terms of imaging techniques, although DXA is the recognized gold standard for the diagnosis of osteoporosis, the use of ionizing radiation is not recommended in pregnancy due to possible deleterious effects on the fetus. As an alternative, the use of QUS could be considered in antepartum women. This inexpensive, radiation-free method provides information on bone properties that are somewhat different to BMD and that may include bone quality.[38]

In the case of postpartum women with persistent severe back pain, conventional X-ray optionally followed by MRI of the thoracic and lumbar spine can be used to determine the presence of fracture. If fragility fractures are present, further assessment follows the same pathway as for antepartum women, other than DXA may be used for imaging.

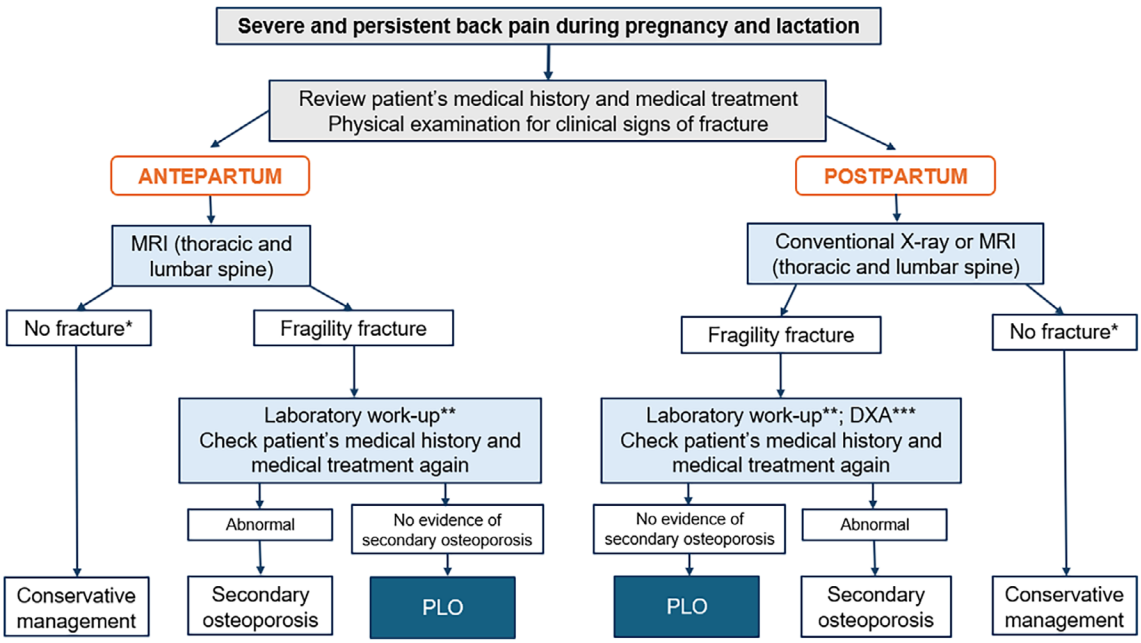

FIGURE 2 Assessment and diagnosis of women with suspected pregnancy- and lactation-associated osteoporosis (PLO). *Consider referral to an orthopedic specialist or traumatologist. **Should include C-reactive protein, complete blood count, calcium, phosphate, alkaline phosphatase, glucose, liver function tests, creatinine, thyroid-stimulating hormone, estrogen, 25-hydroxyvitamin D, parathyroid hormone, and protein electrophoresis. Additionally, the assessment of biochemical markers of bone turnover (CTX, P1NP) might be useful. ***Including vertebral fracture assessment, if available. DXA, dual energy X-ray absorptiometry; MRI, magnetic resonance imaging; PLO, pregnancy- and lactation-associated osteoporosis.

6 | RECOMMENDATIONS FOR TREATMENT AND FOLLOW-UP OF PREGNANCY- AND LACTATION-ASSOCIATED OSTEOPOROSIS

There is currently no standard of care for PLO. In fact, a recent systematic review and meta-analysis of the comparative effectiveness of interventions currently used for PLO concluded that due to heterogeneity of studies and lack of robust comparative data, no definitive conclusions can be drawn regarding the optimal therapeutic choice in this setting.[67] This position statement has been developed based on the available clinical evidence and expert opinion. The treatment and follow-up recommendations below are not intended as formal evidence-based guidelines and, due to the relative rarity of this condition and lack of controlled studies, the available data supporting these has not been assessed and graded for level of evidence.

None of the available pharmacological therapies for osteoporosis is licensed for use in PLO, and so use of any of them in this setting is considered off label. Data on their effectiveness in improving BMD and bone health is mostly drawn from studies in women with postmenopausal osteoporosis and a few observational trials in PLO.

Selection of the most appropriate management approach in women with a confirmed diagnosis of PLO is dependent on pregnancy status (pregnant or postpartum) and the number of vertebral or non-vertebral fragility fractures present (Figure 3). The initial approach in all cases should be to check there is adequate dietary intake of calcium and vitamin D, with supplementation (calcium: 1000–2000 mg/day; vitamin D 1000–2000 IU/day) to ensure a sufficient vitamin D level of >30 ng/mL. However, while most data from randomized controlled trials indicate that vitamin D supplementation during pregnancy has positive effects on the BMD of offspring during childhood, it does not appear to have any specific beneficial effects on the maternal skeleton.[89] Patients with severe and persistent back pain during pregnancy and/or lactation with no vertebral or non-vertebral fragility fracture present should be referred to a specialist for further diagnosis/treatment.

In women with a single vertebral or non-vertebral fragility fracture and any T-score, if available, pain medication and later physiotherapy can be employed, if necessary; in some cases, conservative/operative treatment might also need to be considered. Patients might be encouraged to consider limiting/stopping breastfeeding, which should result in the resumption of menses and a regular menstrual cycle. Patients should be informed about effective methods of contraception (e.g., continuous use of the combined oral contraceptive pill or estradiol-containing oral contraceptives). If after weaning a regular menstrual cycle does not return or there are symptoms of estrogen deficiency, a gynecological consultation should be considered. Further follow-up with BMD and other laboratory assessments

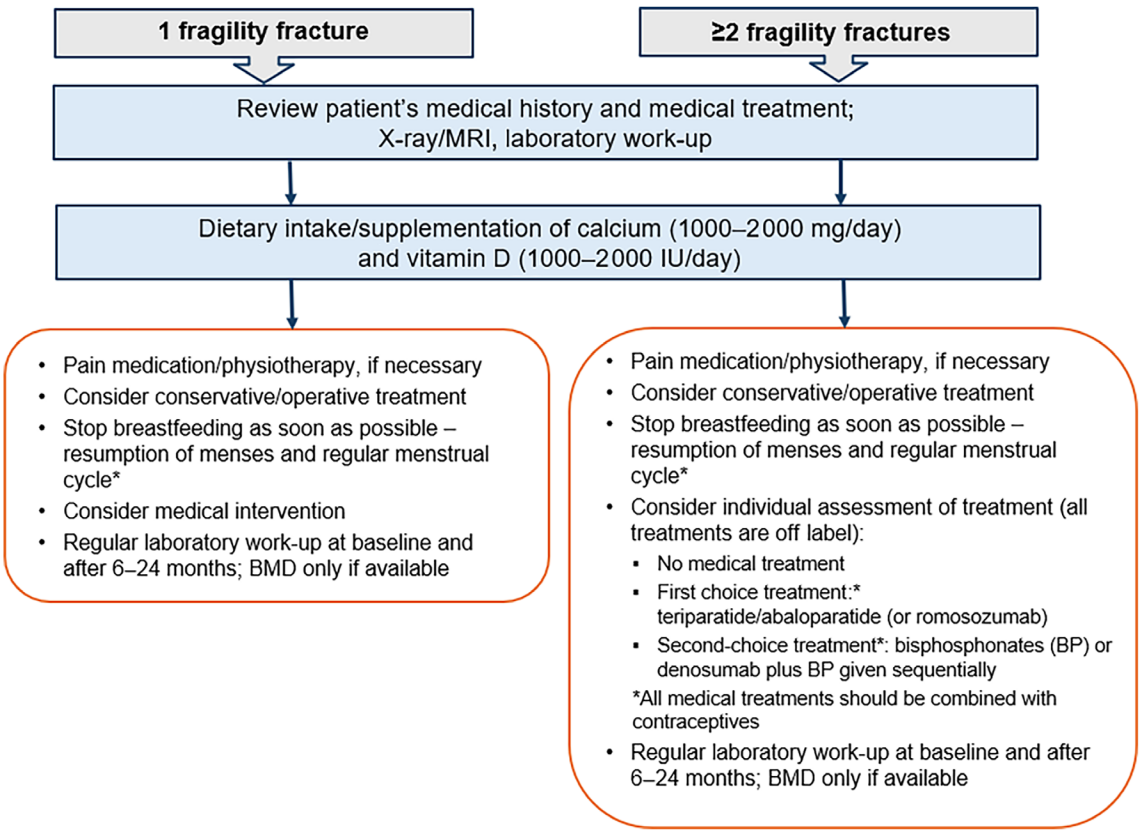

FIGURE 3 Management of women diagnosed with pregnancy- and lactation-associated osteoporosis (PLO) based on the number of fragility fractures. *If after weaning a regular menstrual cycle does not resume, a gynecological consultation should be considered. BMD, bone mineral density; IU, international units; MRI, magnetic resonance imaging.

may be scheduled for 6 months' to 2 years' time, as BMD should at least partially recover. The role of hormone replacement therapy (HRT)/menopausal hormone therapy (MHT) for the treatment of PLO is unknown. HRT/MHT could be considered in the setting of lactation-associated amenorrhea and estrogen deficiency if the woman did not want to cease breastfeeding. Limited data indicated that transdermal estrogen replacement therapy does not adversely affect lactation in women with established lactation.[90] Medical treatment with osteoporosis therapies can be considered, but these may generally be reserved for women with ≥2 vertebral or non-vertebral fragility fractures, regardless of T-score if available. Avoidance of medical treatment is the ideal scenario because all are unlicensed in PLO and their effects on the fetus in future potential pregnancies are not well established. As a result, it is recommended that all medical treatments should be combined with contraceptives, with the exception of the use of DMPA. Although treatment with bisphosphonates has been shown to improve BMD in women with PLO,[67,91,92] they should be avoided where possible as they persist in bone for many years, are able to cross the placenta barrier, and might affect future pregnancies.

It is recommended that in postpartum women with ≥2 vertebral or non-vertebral fragility fractures during pregnancy and/or lactation, the first choice of treatment is teriparatide/abaloparatide or perhaps romosozumab. Teriparatide and abaloparatide are both osteoanabolic agents that mimic parathyroid hormone and are indicated for the treatment of severe osteoporosis in postmenopausal women.[93,94] These are good therapeutic options as they increase bone turnover and BMD, particularly at the spine, where the majority of fractures occur in PLO. The efficacy of teriparatide (a recombinant human parathyroid hormone [PTH 1–34] analog) has been demonstrated in postmenopausal women with multiple vertebral fractures. In the Fracture Prevention Trial (FPT), it was effective in reducing the risk of vertebral and non-vertebral fractures and increasing BMD in postmenopausal women with osteoporosis.[95,96] The FPT follow-up study showed that 18 months after discontinuation of teriparatide treatment, the reduction in vertebral fracture risk was still evident.[97]

There have been some small studies and case reports of the successful use of teriparatide in PLO, as summarized in a review by Ali and colleagues.[98] In a patient with severe PLO and 11 vertebral fractures, teriparatide treatment increased her BMD and she had no further fractures.[99] In a multicenter retrospective cohort study, 19 women with PLO were treated with teriparatide (plus calcium and vitamin D supplementation) for up to 18 months. Teriparatide treatment resulted in significantly greater increases in lumbar spine BMD compared with supplementation alone at 12 and 24 months.[100] A retrospective study evaluated 47 patients with PLO who had suffered multiple vertebral fractures (mean: 4.4 fractures) postpartum and had been referred to the German Reference Center for PLO in Frankfurt between 2004 and 2018.[101] Treatment with teriparatide for 24 months significantly increased BMD, predominantly at the spine, and no significant decrease in BMD was observed in the 12 months following cessation of treatment without any follow-up treatment. When used in PLO and after completion of teriparatide treatment with no subsequent fractures, no follow-up treatment is regularly necessary if the patient has resumed a normal menstrual cycle, as endogenous estrogen is a potent antiresorptive.

Romosozumab is also a possible treatment option in PLO in patients who have either vertebral or non-vertebral fragility fractures, but it has rarely been applied in PLO and should be used with caution.[102–105] Aside from these observations from individual case reports, there is only one single-arm study to date that has evaluated the effect of romosozumab treatment for up to 12 months in a cohort of 29 women with PLO. Romosozumab was associated with large BMD increases at 6 and 12 months, particularly at the lumbar spine, in this cohort. While these findings are promising, they require confirmation in further trials and evaluation of longer-term outcomes.[106]

Denosumab, an antiresorptive agent that blocks RANKL, is a possible second-choice treatment option in this setting. Denosumab reduced the risk of vertebral, nonvertebral, and hip fractures and increased BMD across skeletal sites compared to placebo in clinical trials of postmenopausal women with osteoporosis or low BMD.[107] However, denosumab is associated with a rebound phenomenon whereby cessation of therapy is associated with a rapid increase in markers of bone turnover, loss of BMD, and an increased risk of fractures, in particular multiple vertebral fractures.[108] As a result, sequential treatment with bisphosphonates is usually recommended, but as previously highlighted, they should be avoided, if possible, in PLO. In a case report, denosumab was used successfully to treat a woman with severe PLO and vertebral fractures.[109] After 18 months of treatment with denosumab, a clinically significant increase of BMD was observed at the lumbar spine, femoral neck, and total hip of 32.2%, 13.0%, and 11.5%, respectively, with no further subsequent fractures.

7 | RESEARCH GAPS IN PREGNANCY- AND LACTATION-ASSOCIATED OSTEOPOROSIS

While our understanding of the pathophysiology and treatment of PLO has expanded over the past decade, there are still several gaps in our knowledge regarding this relatively rare but debilitating condition.[110] The epidemiology of PLO has not been widely investigated and studies on the long-term outcomes of women who experience PLO are limited, with only a few studies to date addressing the important clinical question of whether an increased risk of fracture in subsequent pregnancies exists. Similarly, it is still unclear if women who have had PLO in the past are at an increased risk of osteoporosis-related fractures after menopause compared to women who have not had PLO. In the absence of available clinical evidence, ideally an intensified follow-up should be considered in women with a history of PLO (DXA at the time of menopause as well as 2–3 years later). Depending on the individual BMD,

microarchitectural deterioration and existing risk factors, shared decision-making regarding a treatment plan is advised.

Further outstanding clinical questions relate to the optimal contraceptive method during or after weaning, which is still a matter of debate, and the procedure that should be followed after teriparatide treatment in women with PLO and more than two fragility fractures. Is endogenous estradiol in regularly menstruating women sufficient or should a follow-up treatment be advised?

8 | CONCLUSION

PLO is a rare disease in pregnant and lactating women which, in the majority of cases, is identified late, highlighting the need for vigilance among clinicians to ensure that it is correctly identified, properly diagnosed and effectively managed. PLO often presents with multiple – predominantly spinal – fractures that lead to considerable pain and discomfort as well as having severe long-term consequences for the women affected. This position statement includes a pragmatic approach for identifying women with PLO in clinical practice and suggests developing an individualized treatment plan which may include pharmaceutical intervention.

AUTHOR CONTRIBUTIONS

Peyman Hadji: Conceptualization, Writing – original draft, Writing – review and editing. All other authors: Writing – review and editing. All authors meet the qualifications for authorship as detailed in the ICMJE specifications.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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