Original Article

DOI: 10.5582/ddt.2024.01037

Prevalence of pregnancy- and lactation-associated osteoporosis in the postpartum period: A systematic review and meta-analysis

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SUMMARY This systematic review and meta-analysis aimed to estimate the prevalence of pregnancy- and lactation-associated osteoporosis in postpartum women within 1 year of delivery. We searched MEDLINE *via* PubMed and Igaku Chuo Zasshi for articles published in English or Japanese from the inception of the database to September 2021. Two researchers independently screened and included observational studies reporting the prevalence of pregnancy- and lactation-associated osteoporosis in postpartum women within 1 year of delivery. Of the 3,425 screened records, 8 articles centered on postpartum women were included in the review. Seven studies used dual-energy X-ray absorptiometry for assessing bone mineral density, while one used a quantitative ultrasound method. In the seven studies that used dual-energy X-ray absorptiometry, the parameters used to define osteoporosis were the T-score (two studies), Z-score (three studies), both T- and Z-scores (one study), and young adult mean (one study). Evaluation timeframes included 1 week (three studies), 1–2 months postpartum (three studies), and 1 week to 12 months postpartum (one study). The estimated prevalence of pregnancy- and lactation-associated osteoporosis defined by dual-energy X-ray absorptiometry was as follows: lumbar spine (six studies), 5% (95% confidence interval [CI], 0–13; heterogeneity [I^2] = 99%) and femoral neck (three studies), 12% (95% CI, 0–30; I^2 = 99%). Pregnancy and lactation were found to elevate the fracture risk in women, underscoring the necessity for a standardized assessment in diagnosing pregnancy- and lactation-associated osteoporosis. This imperative step aims to enable early detection and treatment of bone mineral loss among postpartum women.

Keywords Bone mineral density, breastfeeding, maternal health, postnatal care, dual-energy X-ray absorptiometry

1. Introduction

Pregnancy- and lactation-associated osteoporosis (PLO) is a condition marked by decreased bone mineral density (BMD) and deterioration of bone structure during late pregnancy and postpartum lactation, elevating the vulnerability to fractures. The decline in BMD typically advances without overt symptoms, leading to a subclinical course that may go unnoticed. PLO diagnosis is often prompted by unexpected fractures, including fragility fractures of the vertebral body or fractures resulting from minor external forces during routine activities. Consequently, healthy pregnant or postpartum women may experience sudden fractures, underscoring the covert nature of PLO onset, evident only with the occurrence of fractures (*1*).

Multiple factors are involved in the pathogenesis of PLO, including the pre-existing risk factors for osteoporosis before pregnancy, alongside the characteristics of bone metabolism during pregnancy and lactation (*2*). Pre-existing risk factors for osteoporosis, such as low peak bone mass due to low body weight or poor nutrition, can increase susceptibility to PLO (*3,4*). Hormonal alterations during pregnancy, particularly elevated estrogen levels, promote bone preservation by inhibiting bone resorption (*5*). However, the placental transfer of calcium from mother to fetus may transiently deplete maternal bone calcium (*6*). Subsequently, a sharp postpartum drop in estrogen levels, coupled with prolonged low levels during lactation, prompts

heightened bone resorption and diminished bone formation, ultimately contributing to PLO. Additionally, the production of breast milk necessitates extra calcium; if maternal calcium intake inadequately satisfies both maternal and infant requirements, calcium demand is met through bone resorption to support milk production, consequently eroding maternal bone density (*7,8*). Complete breastfeeding and increased lactation volume or duration precipitate a more pronounced bone loss due to heightened calcium demand (*5*).

Postpartum fractures not only cause distress to the woman, but the treatment associated with the fracture also affects her quality of life and the health of her infant. Typically, women with postpartum fractures discontinue breastfeeding to curtail heightened bone resorption (*2,9-11*). This interruption places postpartum women at risk for mastitis and deprives infants of the infection-protective benefits inherent in breast milk (*12*). Therefore, preventive care for PLO-related fractures during pregnancy and postpartum is imperative. A systematic review by Qian *et al*. (*3*) focusing on patients with PLO associated with vertebral fractures has reported important information on the clinical manifestations of fractures, risk factors, and treatment options. However, while some PLO patients experience fragility fractures (*i.e.*, overt PLO), many others live with decreased BMD without being aware of their condition (*i.e.*, covert PLO). This oversight regarding the potential impact of pregnancy and lactation on bone health results in undiagnosed patients missing necessary care and intervention.

Addressing this issue necessitates establishing the prevalence of PLO, furnishing healthcare providers with a comprehensive understanding of the scope of the problem and its potential impact on maternal health. Although PLO is predominantly identified after a fracture occurs and the prevalence of PLO with vertebral fractures is currently known to be 4-8 per 1 million pregnancies (*2,3*), the exact prevalence of PLO in individuals who have yet to experience fractures remains unknown. A systematic review by Karlsson *et al*. indicates that BMD diminishes by approximately 5% during pregnancy and a further 5% during the postpartum period to 6 months postpartum (*13*). This suggests that many lactating women are prone to osteoporosis without documented fractures.

Defining methods to measure BMD and establishing diagnostic cutoff values for PLO is necessary to establish standardized guidelines (*14*). Some reports have used existing osteoporosis criteria, such as the World Health Organization (WHO) diagnostic criteria for osteoporosis, specifying a T-score < -2.5 standard deviation (SD) using 20-29-year-old Caucasian women as a reference (*15*) or the Z-score recommended for young adults (*16*). The prevalence of PLO could potentially be approximated from such reports (*4,17*). Consequently, this study aimed to determine the prevalence of PLO in the postpartum phase using these reports.

2. Materials and Methods

2.1. Search strategy and selection criteria

We searched MEDLINE *via* PubMed for articles published in English from the inception of the database until September 2021. Additionally, we searched Igaku Chuo Zasshi (Ichushi Web) to include articles written in Japanese. The following search terms were used: "pregnancy," "postpartum," "lactation," "bone mineral density," and "osteoporosis."

The eligibility criteria for the systematic review were: 1) inclusion of postpartum women within 1 year of delivery as participants, 2) use of BMD as an outcome, and 3) cross-sectional or cohort study design, in which prevalence could be calculated. When several articles used the same dataset, the article with the largest number of participants was selected for systematic review. The search results were de-duplicated using Rayyan (*http://rayyan.qcri.org*) before screening by two researchers.

2.2. Quality assessment and data extraction

Two independent researchers (M. F. and M. K.) screened the titles and abstracts of identified articles, followed by full-text reviews to confirm eligibility based on inclusion criteria. The quality of the articles was assessed using the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS), focusing on six domains: selection of participants, confounding variables, measurement of exposure, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting (*18*). After independent screening and evaluating bias by individuals, the researchers resolved disagreements through discussions.

2.3. Data synthesis and analysis

We conducted a meta-analysis to estimate the pooled prevalence of PLO. Data analysis was performed using the R statistical software (Version 4.4.0; R Foundation for Statistical Computing, Vienna, Austria) in the Google Colaboratory (Google, Mountain View, CA, USA) environment, using the meta package's metaprop function. Event counts and total participants from each study were used to calculate the proportions and their 95% confidence intervals (CIs).

The DerSimonian–Laird random-effects model was applied with the Freeman–Tukey double arcsine transformation to stabilize the variances of the proportions. Heterogeneity among the studies was assessed using the I^2 statistics and τ^2 variance component. Forest plots were generated to visually assess the extent of heterogeneity across the studies.

For all statistical analyses, statistical significance was

set at $P < 0.05$. All analyses were performed using the R statistical software.

3. Results

3.1. Study selection process

Overall, 3,695 records were identified through electronic database searches, and 67 duplicate articles were excluded (Figure 1). The titles and abstracts were screened based on the inclusion and exclusion criteria, and 3,277 records were excluded. Of the remaining 351 studies, full texts were screened, and 344 studies failing to meet the inclusion criteria concerning population and outcome, study design, language, and the non-utilization of the same data source were excluded. Additionally, studies that did not offer adequate information for calculating the prevalence were excluded. After evaluating the quality of the articles using the RoBANS, eight articles that focused on postpartum women were included in the review (Table 1 and Supplementary Figure 1).

3.2. Characteristics of the studies reviewed

Of the eight studies, six excluded women with complications or obstetric diseases and focused on healthy women (*17,22,19,4,20,21*); four of these studies excluded women with diseases or those taking medications that affect bone metabolism (*17,22,20,21*). Of the remaining two studies, one study did not exclude women with complications or obstetric diseases but did exclude those taking medications that affect bone metabolism (*24*). The other study included all women who delivered at the study hospital (*23*).

Seven studies measured BMD using dual-energy X-ray absorptiometry (DXA) and employed the T-score (*19,20*), Z-score (*4,21,22*) both T and Z scores (*23*), and young adult mean (YAM) (*17*), as parameters for the definition of osteoporosis. One study used quantitative ultrasound (QUS) to measure BMD and stiffness index as a parameter to define osteoporosis (*24*).

Six studies measured BMD at the lumbar spine (*4,17,19,20,22,23*), three at the femoral neck (*4,17,23*), two at the hip (*4,17*), one at the trochanter (*4*), one at the distal radius (*21*), and one at the calcaneus (*24*). The assessment periods were 1 month postpartum (*4,19,20,22,23*), 3 months postpartum (*24*), and 1 week to 12 months postpartum (*21*).

3.3. Prevalence of PLO

The estimated prevalence of PLO, measured by DXA, was as follows (Figure 2): lumbar spine (*4,17,19,20,22,23*) at 5% (95% CI, 0-13; $I^2 = 99\%$, $P < 0.01$) and femoral neck (*4,17,23*) at 12% (95% CI, 1-30; $I^2 = 99\%$, $P < 0.01$).

4. Discussion

We conducted a systematic review and meta-analysis to assess the prevalence of PLO in postpartum women. Eight articles were included in this analysis, with seven using DXA for BMD measurement and one employing QUS. Most measurements were conducted approximately 1 month postpartum. The estimated prevalence of PLO during the postpartum period was 5-12%, drawn from six studies that evaluated lumbar spine BMD *via* DXA and three studies that measured femoral neck BMD.

The prevalence of PLO reported in this study was

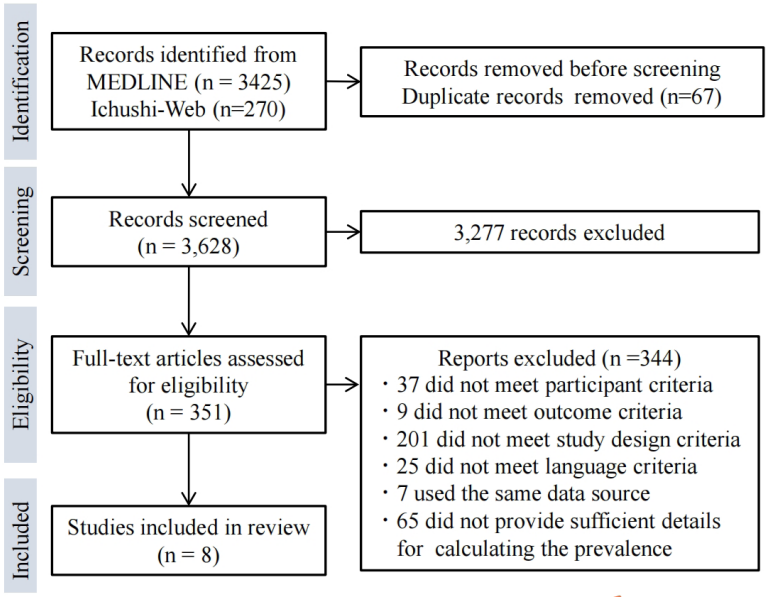

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the study selection process.

Table 1. Characteristics of the studies and prevalence of pregnancy and lactation-associated osteoporosis

Study	Participants	Current and past breastfeeding	Evaluation method	Scale	Time	Prevalence (patient/participant)					
						Lumbar spine	Femoral neck	Total hip	Trochanter	Distal radius	Calcaneus
Kurabayashi T *et al.*, 2021 (*17*) Japan	Age (mean ± SD): 33.5 ± 4.5 years BMI before pregnancy (mean ± SD): Normal 22.5 ± 4.3 kg/m^2, Osteopenia 20.3 ± 2.4 kg/m^2, Osteoporosis 19.3 ± 2.5 kg/m^2 Healthy women with no complications No fractures of the spine or femoral bone Not receiving any medications that would affect bone metabolism before or during pregnancy		DXA	YAM <70% or <−2.5 SD	Within 2–3 days	0.6% (7/1079)	4.8% (52/1079)	1.5% (16/1079)			
Eroglu S *et al.*, 2019 (*22*) Germany	Age (mean ± SD): Normal 30.1 ± 7.2 years, Low BMD 29.1 ± 4.1 years BMI before pregnancy (mean ± SD): Normal 28.0 ± 4.6 kg/m^2, Low BMD 27.6 ± 4.8 kg/m^2 Healthy women aged 18–40 years Not using antiresorptive drugs or receiving vitamin D or calcium medications No acute or chronic infections, history of trauma, psychiatric disorders, or any secondary causes of inflammation	Total breastfeeding month mean (range) Normal: 12 (0–24) Low BMD: 11.5 (0–48)	DXA	Z score ≦−2.0	1 month	30.9% (29/93)					
Kajale N *et al.*, 2016 (*19*) UK	Age (mean ± SD): 27.7 ± 3.5 years BMI at study enrolment: 26.3 ± 4.0 kg/m^2 Primiparous women with singleton pregnancies No pre-existing conditions like gestational diabetes or preeclampsia Not diagnosed with intrauterine growth restriction/ retardation or small for gestational age		DXA	T score <−2.0	Within 7 days	10% (12/128)					
Jang DG *et al.*, 2016 (*4*) Korea	Age (mean ± SD): 32.8 ± 3.9 years BMI before pregnancy (mean ± SD): 20.8 ± 2.6 kg/ m^2 Women who gave birth after 32 weeks of gestation Absence of the following diseases: hyperthyroidism, hypothyroidism, systemic lupus erythematosus, rheumatoid arthritis, insulin-dependent diabetes mellitus, kidney disease, epilepsy, depression, schizophrenia, and hematologic disease Not treated for infertility	Exclusive breastfeeding number (%): 407 (26.1%)	DXA	Z score ≦−2.0	4–6 weeks	13.8% (215/1561)	24.8% (387/1561)	16.4% (256/1561)	24.1% (376/1561)		

YAM, young adult mean; DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; BMI, body mass index.

Table 1. Characteristics of the studies and prevalence of pregnancy and lactation-associated osteoporosis (continued)

Study	Participants	Current and past breastfeeding	Evaluation method	Scale	Time	Prevalence (patient/participant)					
						Lumbar spine	Femoral neck	Total hip	Trochanter	Distal radius	Calcaneus
Lebel E *et al.*, 2014 (*23*) Israel	Age (mean ± SD): 29.9 ± 6.0 years BMI before pregnancy (mean ± SD): 24.2 ± 4.4 kg/m^2 History of fracture: 14 (10.6%) All women who remained in the hospital postpartum (up to 48 h)	Total breastfeeding month Mean ± SD (range): 27.09 ± 31.61 (0–135.0)	DXA	T score and/or Z score <−2.0	Within 48 h	0% (0/132)	9.1% (12/132)				
Kurabayashi T *et al.*, 2009 (*20*) Japan	Age (mean ± SD): 31.3 ± 4.7 years BMI before pregnancy (mean ± SD): Normal 23.0 ±2.9 kg/m^2, Osteopenia 21.6 ± 2.4 kg/m^2, Osteoporosis 20.9 ± 1.8 kg/m^2 Healthy Japanese women with no complications aged 17–46 years No obstetric complications that required prolonged bed rest during pregnancy No history of excessive caffeine intake Not receiving medications that would affect bone metabolism before or during pregnancy		DXA	T score <−2.5 SD	Within 7 days	0.3% (8/2436)					
Costa ML *et al.*, 2012 (*21*) Brazil	Age (mean ± SD): 26.4 ± 6.4 years Weight before pregnancy: (mean ± SD): 62.5 ± 12.3 kg Healthy postpartum women with no complications aged 18–40 years who had a singleton delivery after 37 weeks Intend to delay their next pregnancy for at least 12 months postpartum No history of diseases before or during pregnancy that would affect calcium or bone metabolism Not receiving any of the following medications: corticosteroids, anticoagulants, anticonvulsants, thiazide diuretics, and drugs for the treatment of thyroid disease	Duration of exclusive breastfeeding days mean (SD): 125.9 (±66.6) days 0–3 months; 24 (30.8) 3–6 months; 45 (57.7) >6 months; 9 (11.5)	DXA	Z score <−2.0	7–10 days 3 months 6 months 12 months					1.3% (13/100) 2.6% (2/91) 3.8% (3/84) 3.8% (3/78)	

YAM, young adult mean; DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; BMI, body mass index.

Table 1. Characteristics of the studies and prevalence of pregnancy and lactation-associated osteoporosis (continued)

Study	Participants	Current and past breastfeeding	Evaluation method	Scale	Time	Prevalence (patient/participant)					
						Lumbar spine	Femoral neck	Total hip	Trochanter	Distal radius	Calcaneus
Hoshino A *et al.*, 2017 (*24*) Japan	Age [median (25th, 75th percentiles)]: 33 (30, 36) years BMI at study enrolment [median (25th, 75th percentiles)]: 20.4 (19.2, 21.9) History of fracture: 268 (22.1%) Women aged <45 years who had singleton deliveries No history of receiving medications affecting bone mass	Mainly breastfeeding number (%): 987 (80.9%)	Quantitative ultrasound	Stiffness score <70.1	3–4 months						10.9% (133/1220)

YAM, young adult mean; DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; BMI, body mass index.

based on combined results from studies that focused on postpartum women who lacked any pre-existing risk factors for osteoporosis before pregnancy, including medication-induced impacts on bone metabolism or a history of metabolic bone disease (*4,17,19,20,22,23*). While the included studies targeted healthy postpartum women, the prevalence of osteoporosis in this group surpassed that reported in a meta-analysis, which indicated a 3% osteoporosis prevalence in premenopausal women (*25*). This study highlights the heightened fracture risks by pregnancy and lactation compared with women of equivalent age. Recognizing the negative implications of fractures on maternal and infant health renders BMD screening and early detection of decreased BMD or women susceptible to PLO-related fractures during the postpartum phase justifiable.

The pathogenesis of postpartum osteoporosis is linked to the decline in postpartum estrogen and heightened bone resorption to fulfill infant calcium requirements (*26*). Our study aimed to ascertain osteoporosis prevalence in postpartum women within the first year of postpartum, considering the influence of the lactation period. However, six of the eight studies (*4,17,19,20,22,23*) were included in the systematic review, and five of the six studies included in the meta-analysis (*17,19,20,22,23*) were conducted within 2 months postpartum. Therefore, the reported 5-12% prevalence of PLO primarily reflects the early postpartum phase and may not truly represent the entire lactation duration. Sowers *et al.* reported that women lactating for over 6 months experienced a bone loss of 4.8% in the femoral neck and 5.1% in the lumbar spine. In contrast, no significant BMD change was observed for short-term lactation within 1 month or less (*27*). Consequently, the peak prevalence of PLO might be higher during the first postpartum year than that indicated in this study. Given the complexity of postpartum hormonal changes and their potential impact on bone health, further research is needed to comprehensively elucidate the prevalence and trajectory of PLO throughout the entire lactation period.

The estimated prevalence of osteoporosis in postpartum women was 5-12%; however, the I^2 test unveiled a high heterogeneity of 99%. One factor contributing to this heterogeneity is the diversity in definitions of osteoporosis used in the studies included in the meta-analysis. This disparity in definition can be attributed to the absence of standardized diagnostic criteria tailored specifically for PLO. Of the eight articles included in this meta-analysis, two used T-scores, three used Z-scores, one used both T- and Z -scores, one used YAM values, and one used stiffness values.

The absence of consensus on PLO diagnostic criteria and the definition of osteoporosis in young adults contributes to methodological heterogeneity across studies (*14*). The WHO diagnostic criterion for osteoporosis is defined as a T-score < -2.5 SD (using 20–29-year-old Caucasian women as a reference) (*15*).

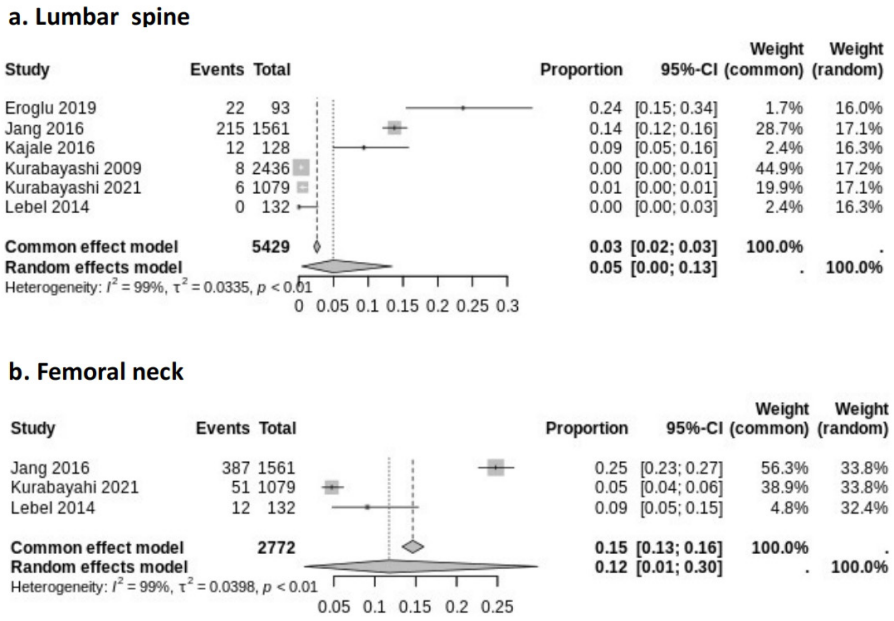

Figure 2. Prevalence of pregnancy- and lactation-associated osteoporosis (a. lumbar spine b. femoral neck). CI, confidence interval.

However, this diagnostic criterion is mainly tailored to postmenopausal osteoporosis. The International Society for Clinical Densitometry suggests diagnosing osteoporosis in young adults with a Z-score < − 2.0 SD in comparison to the mean age-, sex-, and ethnicity-matched reference population (*16*). On the contrary, the International Osteoporosis Foundation recommends using a T-score < − 2.5 SD for osteoporosis diagnosis in young adults, particularly in cases that involve factors affecting bone mass (*28*). The broad spectrum of prevalence estimates for PLO and the substantial heterogeneity across studies underscore the need for consensus and the establishment of standardized diagnostic criteria for PLO. Furthermore, establishing clear criteria for osteoporosis in young adult women would bolster the comparability and reliability of future research in this area.

The high heterogeneity across studies may also stem from the variability in the timing of osteoporosis evaluations, spanning from 48 h to 6 weeks postpartum. This interval coincides with substantial physiological shifts, encompassing modification in breast-milk supply and calcium demands essential for lactation. In cases of complete breastfeeding, the supply of breast milk to the infant increases from approximately 5–30 mL/day in the first few days postpartum to 750–800 mL/day in the first 1–2 months postpartum, with a calcium supply ranging from 280–400 mg/day. Notably, studies conducted 2 months postpartum (*4,22*) yielded a higher osteoporosis prevalence than those conducted within a few days postpartum (*17,19,20,23*). This suggests that the disparity in prevalence could be attributed to fluctuations in calcium loss during the postpartum period. However, because of the limited number of included studies and the absence of lactation information, our review could not perform a stratified analysis based on the postpartum period. Additional reports and further analyses are necessary to better understand the influence of postpartum timing on osteoporosis prevalence.

The considerable prevalence of osteoporosis demonstrated in this study highlights the necessity for BMD screening in postpartum women. Although DXA remains the gold standard for BMD evaluation, limitations related to its lack of portability, cost, and radiation exposure warrant consideration of alternative methods (*15*). Our review identified one report of prevalence assessed using QUS of the calcaneus (*24*). While direct comparisons of prevalence rates among studies must be approached cautiously, the reported PLO prevalence using QUS was higher than that using DXA in our meta-analysis. Thus, QUS might overestimate the risk of PLO; however, it could serve as a useful method for screening women with covert PLO because screening methods should not overlook those at risk. Importantly, compared with DXA, QUS of the calcaneus is radiation-free, more cost-effective, and exhibits potential for osteoporosis screening (*29-31*). Validating the utility of QUS for diagnosing postpartum women may lead to the establishment and widespread adoption of PLO screening methods.

This study had a few limitations. First, it solely included articles that described the number of patients using the osteoporosis definition and were able to calculate prevalence. Most studies that measure BMD in postpartum women provide actual values or changes in BMD but lack patient numbers or prevalence. Second, while this study encompassed women within 1 year postpartum, most studies were conducted in the early postpartum period, with only one being a cohort study. Consequently, variations and changes in

PLO prevalence during the postpartum period remain unknown. Additionally, whether pregnancy and lactation affect BMD and if patients might have had osteoporosis before pregnancy remains uncertain. Third, this study did not explore factors contributing to osteoporosis, such as feeding methods (breastfeeding or formula feeding) or menstrual status. Future studies should include subgroup analysis stratified by the postpartum period and osteoporosis-related factors.

In conclusion, this systematic review and meta-analysis revealed that the prevalence of PLO during the postpartum period ranges from 5 to 12%. Nevertheless, caution must be exercised regarding the accuracy of these estimated figures because of differences in the definition of osteoporosis owing to the lack of standardized diagnostic methods for PLO. Thus, it is imperative to establish a standardized diagnostic method for PLO, conduct further research, and implement early detection and intervention measures through screening in the future.

Funding: This work was supported by JSPS KAKENHI (grant number: 20K23218). The sponsors had no role in the design, execution, interpretation, or writing of the study.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received May 31, 2024; Revised July 30, 2024; Accepted August 20, 2024.

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Released online in J-STAGE as advance publication August 25, 2024.