Pregnancy- and Lactation-associated Osteoporosis with Vertebral Fractures: A Systematic Review

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Abstract

**Background**: To review, analyze and characterize the pregnancy and lactation-related osteoporosis (PLO) with vertebral fractures based on the extraction data in the previous studies.

**Methods**: A comprehensive literature search of electronic databases including the PubMed, Embase and Web of Science was conducted from January 1st, 1990 to December 1st, 2020. The enrolled data were pooled to analyze the baseline characteristics, clinical features, risk factors and treatment options.

**Results**: A total of 65 articles with 338 cases were enrolled for data extraction. The enrolled cases aged from 19 to 47 years, with a mean value of 35.7 years old. The average body mass index (BMI) was 22.2kg/m² ranged from 16.0 to 39.0 kg/m². Of the 173 cases, 149 cases with vertebral fractures occurred in the first pregnancy, 19 cases in the second pregnancy, four cases in the third pregnancy and one case in the fourth pregnancy. Up to 91.5% of the back pain occurred within the last three months of pregnancy and the first three months after delivery. The most involved vertebral levels were L2, L1 and T12 accounting for 32.6% of all the fractures. The average fracture numbers were 4.4 levels per patient. The lumbar Z-scores were mostly recorded with a mean value of -3.2 ranged from -7.8 to 0.

**Conclusions**: PLO with vertebral fractures is a rare clinical entity, which is more likely to occur in older and thinner pregnant women. Back pain is the clinical complaint and mostly occurs in the late pregnancy and early lactation periods. Most vertebral fractures appear in the first pregnancy but it can occur in any time of pregnancy. Thoracolumbar region is the mostly involved region. As compared with postmenopausal osteoporotic fractures, PLO usually has multiple levels fractures. Bisphosphonates are the most widely used treatment so far, but teriparatide has become an effective alternative to bisphosphonates.

Background

Pregnancy- and lactation-associated osteoporosis (PLO) is a rare type of osteoporosis that often occurred during the late pregnancy and early lactation [1–4]. Epidemiological data on PLO are limited although previous study has estimated that the prevalence was 4–8 patients per million of population [5]. Back pain is one of the most common clinical manifestation and many patients may suffer from vertebral fractures or even kyphosis. PLO carries great physiological and psychological burdens to patients and has positive effects on quality of life and working ability. It was reported that the mean time for the PLO patients returned to work was more than three years [6].

Since the first report in 1955 by Nordin, many studies have reported this clinical entity [1–4, 6–19]. Because of the relatively low incidence, most of the studies were case reports and case series, and the clinical features were systematically varied. The patients had experienced back pain differently. Pain can vary from mild to severe and the manifestations of PLO can be present in different trimester of pregnancy. Certain PLO cases occur in the first pregnancy and some occurred in the fourth pregnancy [20]. The patients may have modifiable risk factors like prior fractures history [21, 22], taking drugs affecting bone metabolism [23–25] and smoking, and non-modifiable risk factors like having family history of osteoporosis [6, 17, 26], and have no risk factors. There is no specific department for PLO. Patients may have attended the Department of Endocrinology, Orthopedics or Obstetrics and Gynecology, however, due to the study limitations and poor awareness, many clinicians have imposing appropriate diagnostic delay and may result in poor prognosis.

In order to enhance the knowledge on PLO with vertebral fractures, a systematic review was conducted. We aimed to characterize the clinical manifestation, risk factors, fracture sites and treatment options of PLO based on a data extraction file.

Methods

**Search Terms**

A comprehensive literature search of electronic databases including the PubMed, Embase and Web of Science was conducted on December 1st, 2020 to retrieve all articles reporting PLO. The search strategy utilized the following key terms: “Pregnancy OR pregnant OR lactation OR breastfeeding”, “Osteoporosis OR osteoporotic”, “Vertebra OR spine OR spinal OR lumbar OR thoracic OR thoracolumbar”, “Fracture OR fractures”. The search terms were simply contained in the words of the title and abstract of the Pubmed and Embase and in topic terms in the Web of Science. The cases reported in the early literature were seldom diagnosed by using MRI for vertebral fractures, therefore we only included studies published after January 1st, 1990.

**Inclusion and Exclusion Criteria**

The inclusion criteria included all articles on PLO published in English. Exclusion criteria were: 1) basic research; 2) editorials, letters or meeting abstract; 3) studies that could not found full-text; 4) inadequate information; 5) vertebral fractures that had no direct connection with pregnancy; 6) vertebral fractures occurring during pregnancy or lactation but having underlying diseases that led to osteoporosis.

**Data Extraction**

The retrieved articles were examined and reviewed independently by two researchers. Duplicates were removed automatically by EndNote X8.1 and manually by comparing authors, titles and date of the publications. After the removal of duplicates, title, abstract and full text of articles were screened. Articles reporting the same cohort were also excluded. Then, the supplement search of the references in all the enrolled articles was performed. Data extraction of the selected articles was conducted by two authors using a standard table based on the Cochrane Handbook. For those articles reporting case series, data
extractions were performed only in those cases with vertebral fractures. Any disagreements were resolved by a third researcher. In order to unify the standard, the age at onset of symptoms and the height before pregnancy were recorded.

Results

Studies selection process

At the initial, 458 articles were retrieved from the database searching, 307 of which remained after duplicates removed. After removing meeting abstract, editorial material and letters, 292 articles were obtained. Of these, 209 were excluded since they did not meet the inclusion criteria. After full text articles assessed for eligibility, another 18 articles were excluded. Finally, 65 articles with 338 cases were enrolled in this systematic review for further data extraction. The flow chart shown in Figure 1 demonstrates the selection process in detail.

Study characteristics

Baseline characteristics are showed in Table 1. All the enrolled studies were case report and case series with the case number ranged from 1 to 107 patients. Kyvernitakis[1] reported the most cases numbered at 107 based on the German reference center for PLO and Laroche[2] reported the subsequent most cases numbered at 52 based on the French Society of Rheumatology. The number of articles published increased year by year, with 9 articles from 1991 to 2000, 13 articles from 2001 to 2010, and 43 articles from 2011 to 2020. The enrolled studies distributed globally with 34 studies in Europe, 17 studies in Asia, 5 studies in Australia, 5 studies in South America, 3 studies in North America and one study in Africa. Turkey had the highest number of PLO articles which 11 articles were recorded, followed by Germany with 8 articles and Italy (n = 7) and South Korea (n = 7).
Table 1
The enrolled studies and baseline characteristics of the enrolled cases

| Number | First author | Location | Published year | Journal             | No of Cases | Race          | Age at onset(years) | Height(cm) | Weight(kg) | BM |
|--------|--------------|----------|----------------|---------------------|-------------|---------------|--------------------|------------|------------|----|
| 1      | Tuna         | Turkey   | 2020           | Gynecol Endocrinol  | 9/14        |               | 31                 |            |            | 21 |
| 2      | Hardcastle   | UK       | 2019           | Osteoporos Int      | 10          | Moroccan      | 33                 |            |            | 23 |
| 3      | Scott        | Australia| 2019           | Osteoporos Int      | 1           | Caucasian     | 33                 | 162        | 74         | 28 |
| 4      | Ozturk       | Turkey   | 2019           | Gynecol Endocrinol  | 2           |               | 33,28              |            |            | 27 |
| 5      | Gehlen       | Germany  | 2019           | Clin Rheumatol      | 20          |               | 33.9±27-42±       |            |            | 23 |
| 6      | Zhu          | Australia| 2018           | Osteoporos Int      | 2           |               | 29                 |            |            | 29 |
| 7      | Li           | China    | 2018           | Clin Rheumatol      | 10/12       | Han,1Manchu   | 31                 |            |            | 21 |
| 8      | Hong         | Korea    | 2018           | Clin Endocrinol     | 32          |               | 31.3 ± 2.6         |            |            | 20 |
| 9      | Butscheidt   | Germany  | 2018           | Osteoporos Int      | 5/7         |               | 35                 |            |            | 22 |
| 10     | Taraktas     | Italy    | 2018           | Turk J Endocrinol   | 1           |               |                    |            |            | 22 |
| 11     | Yun          | Korea    | 2017           | Obstet Gynecol Sci  | 6           |               | 32                 | 164        | 57         | 21 |
| 12     | Kyvernitakis | Germany  | 2017           | Osteoporos Int      | 107         |               | 39.5±6.0           | 165.9+/63; | 63.5+/-11.1| 23 |
| 13     | Zhang        | China    | 2017           | Medicine            | 1           |               | 23                 |            |            | 21 |
| 14     | Laroche      | France   | 2017           | Osteoporos Int      | 52          |               |                    |            |            | 27 |
| 15     | Ljuin        | Japan    | 2017           | Taiwan J Obstet Gynecol | 1       |               | 27                 | 163        | 45         | 17 |
| 16     | Pola         | Italy    | 2016           | J Biol Regul Homeost Agents | 1 | Caucasian     | 33                 | 167        | 60         | 21 |
| 17     | Krishnakumar | India    | 2016           | J Craniovert Jun Spine | 2       |               | 27,31              |            |            |    |
| 18     | Sánchez      | Argentina| 2016           | Clin Cases Miner Bone Metab | 2 |               | 35,33              | 162157     |            |    |
| 19     | Grana        | Italy    | 2016           | Pain Med            | 1           | Caucasian     | 31                 |            |            |    |
| 20     | Gaudio       | Italy    | 2016           | Clin Cases Miner Bone Metab | 1 |               | 38                 | 167        | 54         |    |
| 21     | Ekim         | Turkey   | 2016           | J Clin Anal Med     | 1           |               | 35                 | 165        | 54         |    |
| 22     | Polat        | Turkey   | 2015           | Gynecol Endocrinol  | 1           |               | 23                 |            |            |    |
| 23     | Hadgaonkar   | India    | 2015           | Asian Spine J       | 1           |               | 24                 |            |            |    |
| 24     | Ozdemir      | Turkey   | 2015           | Osteoporos Int      | 2           |               | 34,36              | 168,162    | 62,59      |    |
| 25     | Kovacs       | Canada   | 2015           | Osteoporos Int      | 1/2         |               | 35                 | 151        | 46         |    |
| 26     | Grizzo       | Brazil   | 2015           | Calcif Tissue Int   | 1           | Caucasian     | 31                 | 165        | 55         |    |
| 27     | Zarattini    | Italy    | 2014           | Clin Cases          | 1           | Caucasian     | 27                 | 165        | 63         |    |
|   | Author         | Country | Year | Journal                                      | Type | Caucasian | Asian | European | African | Others   | Total |
|---|----------------|---------|------|----------------------------------------------|------|-----------|-------|----------|--------|----------|--------|
| 28| Takahashi      | Japan   | 2014 | Fukushima J Med Sci                         | 1    | 22        | 163   | 60       | 22     |          |        |
| 29| Obando         | Netherlands | 2014 | J Clin Endocrinol Metab                     | 1    | Caucasian | 27    | 158      | 53     | 21       |        |
| 30| Raffaetà       | Italy   | 2014 | Clin Cases Miner Bone Metab                 | 2    | 42,21     | 167   | 66       | 23     |          |        |
| 31| Ozturk         | Turkey  | 2014 | J Obstet Gynaecol                           | 2    | 22,34     |       |          |        |          |        |
| 32| Baldane        | Turkey  | 2014 | Turk Fiz Tip Rehabil Derg                  | 1    | 35        | 155   | 45       | 18     |          |        |
| 33| Winarno        | Germany | 2014 | Z Geburtsh Neonatal                         | 1    | 29        | 158   | 46       | 18     |          |        |
| 34| Terzi          | Turkey  | 2014 | BioMed Res Int                              | 1    | 32        |       |          |        |          |        |
| 35| Cook           | USA     | 2014 | J Bone Miner Res                            | 1    | Caucasian | 26    | 161      | 68     | 26       |        |
| 36| Scozzari       | Italy   | 2014 | Acta Medica Mediterranea                   | 1    | 19        |       |          |        |          |        |
| 37| Lee            | Korea   | 2013 | J Bone Metab                                | 1    | 39        | 156   | 50       | 20     |          |        |
| 38| Bonacker       | Germany | 2013 | Arch Orthop Trauma Surg                    | 1    | 40        |       |          |        |          |        |
| 39| Lwamoto        | Japan   | 2012 | Ther Clin Risk Manag                        | 1    | 32        | 155   | 57       | 23     |          |        |
| 40| Adamidou       | Greece  | 2012 | Horm-Int J Endocrinol Metab                | 1    | Caucasian | 40    | 158      | 56     | 22       |        |
| 41| Choe           | Korea   | 2012 | J Bone Miner Metab                          | 3    | 36,32,30  |      |          |        |          |        |
| 42| Stupar         | Serbia  | 2012 | Rheumatol Int                               | 1    | 30        | 152   | 52       | 22     |          |        |
| 43| Lee            | Korea   | 2011 | J Back Musculoskelet Rehabil                | 1    | 31        | 157   | 50       | 20     |          |        |
| 44| Mastaglia      | Argentina | 2010 | Osteoporos Int                              | 1    | 20        |       |          |        |          |        |
| 45| Kim            | Korea   | 2010 | J Korean Neurosurg Soc                      | 1    | 35        | 150   | 42       | 18     |          |        |
| 46| Hellmeyer      | Germany | 2010 | Gynecol Endocrinol                         | 1    | 40        | 171   | 62       | 21     |          |        |
| 47| Tanriover      | Turkey  | 2009 | Spine J                                     | 1    | Caucasian | 23    | 169      | 65     | 22       |        |
| 48| Jang           | Korea   | 2009 | Rheumatol Int                               | 1    | 30        | 163   | 52       | 19     |          |        |
| 49| Ofuoglu        | Turkey  | 2008 | Rheumatol Int                               | 1    | 30        | 162   | 50       | 19     |          |        |
| 50| Stumpf         | Germany | 2007 | Adv Med Sci                                 | 2    | 32,41     |       |          |        |          |        |
| 51| Hellmeyer      | Germany | 2007 | Exp Clin Endocrinol Diabet                 | 1    | 28        | 158   | 46       | 18     |          |        |
| 52| O’Sullivan     | New Zealand | 2006 | Osteoporos Int                              | 10   | 9Caucasian,1Fijian | 31     |          |        |          |        |
| 53| Bayram         | Turkey  | 2006 | Joint Bone Spine                            | 1    | 37        |       |          |        |          |        |
| 54| Allali         | Morocco | 2005 | Clin Rheumatol                              | 1    | 38        |       |          |        |          |        |
| 55| Tran           | Australia | 2002 | Intern Med J                                | 3    | 2Caucasian | 23,22,36 | 157,170,160 | 47,48,47 | 19       |        |
| 56| Peris          | Spain   | 2002 | Clin Exp Rheumatol                          | 5    | 31        | 155   | 54       | 22     |          |        |
Baseline characteristics of enrolled cases

All the enrolled PLO patients aged 19 to 47 years. A total of 191 cases documented the detailed age information with a mean age of 35.7 years. Of the 191 cases, 6 cases over 40 years old accounting for 3.1%, 109 cases over 30 years old accounting for 57.1%, 29 cases under 26 years old accounting for 15.2%. The age distributions are illustrated in Figure.2. The average height of the included cases is 164.2cm, ranged from 144cm to 175cm. The body mass index (BMI) of 46 studies was calculated and documented with a mean value of 22.2 kg/m$^2$ ranged from 16.0 kg/m$^2$ to 39.0 kg/m$^2$. The BMI distributions of 98 individuals are showed in Figure.3. The observed data showed that few PLO patients were obese and overweight. Furthermore, race information of 38 cases was documented, which was Caucasians (n = 26), Hans (n = 9), Manchu (n = 1), Fijian (n = 1) and Moroccan (n = 1).

Clinical features

A total of 173 cases had the information on number of pregnancy when vertebral fractures occurred, in whom 149 cases were in primiparity, 19 cases were in the second pregnancy, 4 cases were in the third pregnancy and one case was in the fourth pregnancy. There were 108 cases clearly defined feeding manner, with 102 cases breast-feeding accounting for 94.4%. Up to date, not much literature described the delivery way, in which there were vaginal delivery (n = 11) and cesarean delivery (n = 5).

All the included PLO patients with vertebral fractures were symptomized with back pain. The visual analogue score (VAS) were documented in 17 cases, of which all suffered from mild to severe pain and eight cases (47.1%) complained of severe pain. The earliest time of symptom onset was determined at the 5th month pregnancy, while the latest was at nine months postpartum. Of the 82 cases with definite symptom onset time, 75 cases (91.5%) with back pain occurred during the last three months of pregnancy and the first three months after delivery. The details of distributions are shown in Figure.4.

The risk factors associated with PLO were examined such as drug affecting bone metabolism, pre-partum fractures history, family history of osteoporosis, smoking and abnormal menstruation. A total of 59 patients had provided accurate medication history, of which 17 patients (28.8%) had a history of oral anticoagulants such as heparin, low molecular weight heparin (LMWH) and four patients had a corticosteroids history. Of the 68 cases with pre-partum fractures history documented, 17 (25%) cases were suffered from bone fractures before pregnancy. Regarding to family history of osteoporosis, of all the 172 cases with definite documentation, 57 patients (33.1%) had positive family history of osteoporosis. Smoking status was recorded for 111 cases, in which 24 cases (21.6%) were smokers and ex-smokers. There are less menstruation records in the studies, 4 of 25 cases presenting irregular menses.

The studied articles have indicated variable rates of vertebral fractures. Fracture sites were described in 155 cases with 684 vertebral fractures and the average fracture was 4.4 vertebrae per patient. Most cases were suffered from multiple vertebral fractures with only 14 single segment vertebral fractures. As for specific fracture locations, the three most frequently involved vertebral fractures were L2, L1 and T12 (32.6% of all the fractures). The number and site of fractured vertebrae are shown in Figure.5.

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Another important factor is Body mineral density (BMD). BMD values of the enrolled cases were analyzed. $Z$-scores have been preferable used in the studies as compared to $T$-scores. The lumbar $Z$-scores were recorded in 123 cases in mean value of -3.2 ranged from -7.8 to 0, while the hip $Z$-score were recorded in 122 cases with an average of -2.2 ranged from -5.5 to 0.9. The lumbar $T$-scores were recorded in 51 cases with an average of -3.6 ranged from -6.5 to -1.3, while the average of the hip $T$-scores of 47 cases was -2.5 (ranged from -6.5 to -0.2).

Treatment options
Different therapies that have been used in the management of PLO were documented in 108 cases. These therapies included Calcium and vitamin D therapy (n = 7), bisphosphonates (n = 58), teriparatide (n = 24), denosumab (n = 10), calcitonin (n = 6), strontium ranelate (n = 2), simple rehabilitation without medication (n = 2, with mild symptoms) and vertebroplasty (n = 4, with severe symptoms).

Discussion
The current study demonstrated that PLO is a rare clinical entity and distributed worldwide. To date, although more and more reports are available, the documentation of PLO is still very limited and its mechanism remains unclear. The pooled data revealed PLO is more likely appeared in those pregnant women of advanced maternal age. PLO is an age-related disease. Pregnant women in more than half of the cases were over 30 years. Therefore, wide age range of the enrolled pregnant or postpartum women with acute back pain should be excluded from the study.

Similar to postmenopausal osteoporosis, BMI may contribute to increasing risk of PLO. People who are obese or overweight have relatively higher risk of getting PLO.

In general, pregnant women experience calcium loss during the late pregnancy and postpartum lactation. BMD of pregnant women might be associated with pregnancy. In the study of Martina et al (2010), the prospective changes of BMD with an ultrasonometry measurement in 59 pregnant women were observed. The results showed that BMD was reduced significantly in the second and third trimester of pregnancy [27]. This study indicated that osteopenia is a common condition in pregnant women. However, it is difficult and unethical to measure BMD of pregnant women by X-ray or CT. Contrarily, Lebel et al (2014) studied the T-scores and Z-scores of the first 2 days after delivery in 132 pregnant women and found that both scores were within the normal limits regardless of age [28]. These findings indicated that the exact bone metabolism would be more sophisticated in pregnant women.

The pooled data also revealed that PLO may not appear in the first pregnancy. It might be occurred in the second, third or even fourth pregnancy. For patients with multiple pregnancies, PLO might appear in one of them, while other pregnancies were normal [20].

Fracture sites were analyzed in the present study. As compared with other osteoporotic vertebral fractures, PLO had more vertebrae involved. Only a few patients had a single level vertebral fracture. Thoracolumbar region is remained as the most affected area. Magnetic resonance imaging (MRI) should be recommended to detect the conditions of thoracic and lumbar vertebrae if cases of missed diagnosis of the fractured vertebrae for the patients with suspected PLO occurred.

Despite its common occurrence, there is no standard clinical guideline for the treatment of PLO. The current review exhibited various drugs have been used in clinical practice for the treatment of PLO such as bisphosphonates, teriparatide, denosumab and calcitonin. Among the drugs, bisphosphonates are the mostly used. The safety of PLO therapy always is the major concern of clinicians and patients because of its long-term calcium deposits to the bone. The use of bisphosphonates may develop adverse effects on both the fetus and the mother. However, so far, no adverse effects of bisphosphonates on the pregnancy were reported. Due to unforeseen circumstances of bisphosphonates, teriparatide, which helps to regulate calcium metabolism, has been used more frequently for PLO.

Conclusion
PLO is a rare clinical type of osteoporosis, which is more likely occur in older and thinner pregnant women. Back pain is a common clinical manifestation during the last three months of pregnancy and the first three months after delivery. Most PLO occurs in the first pregnancy but it may appear at different stages of pregnancy. Thoracolumbar region is the mostly affected region, however, as compared with postmenopausal osteoporotic fractures, PLO usually has multiple levels fractures. Presently, bisphosphonates are the most widely used treatment for PLO, however, due to the increased of clinical concern, teriparatide has been used as it is an effective alternative to bisphosphonates.

Declarations
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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
Weimin Huang conceived the idea and contributed to design. Weimin Huang and Ying Qian ran the searches and extracted data. Weimin Huang and Lei Wang assessed the methodological quality. Weimin Huang and Lili Yu conducted the meta-analysis. Weimin Huang and Ying Qian wrote the manuscript. All authors
approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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Figures

![Flow diagram of included and excluded studies](image-url)

**Figure 1**
The flow diagram of included and excluded studies
Figure 2
The age distributions of the enrolled cases

Figure 3
The BMI distributions of the included cases
Figure 4
Symptom onset time of the enrolled patients

Figure 5
The fractured site of the enrolled cases

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- [Rawdata.xlsx](#)