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Pregnancy- and lactation-associated osteoporosis: a narrative mini-review

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Abstract. Pregnancy and lactation represent stress states for maternal health and development. Pregnancy and lactation-associated osteoporosis (PLaOs) are uncommon and rare conditions characterized by the occurrence of fragility fracture(s), most commonly vertebral, in late pregnancy or during the postpartum period. The etiology and pathogenesis of these conditions is not clear and several theories are proposed. Due to the rarity of the disease, various isolated clinical cases are reported in the medical literature and only one case-control study thus far. In the current review we try to analyze the pathophysiologic pathways implicated in these conditions and provide possible explanations regarding etiology; we present data on the epidemiology, clinical course, diagnosis and current approved treatment modalities of PLaOs.

Key words: bone density, breast feeding, female, osteoporosis, pregnancy complications, puerperal disorders

Introduction

Pregnancy and lactation are characterized by significant changes in calcium and bone homeostasis; apparently this occurs due to increased fetal demand of calcium for skeletal bone calcification (Rizzoli and Bonjour 1996). Longitudinal monitoring of bone biochemical markers during pregnancy has shown loss of maternal bone usually during the third trimester of pregnancy. Osteoporosis is generally defined as an age-related disorder characterized by decreased bone mass and increased bone fragility in the absence of other recognizable causes of bone loss (Lappe 1994). Pregnancy and lactation-associated osteoporosis (PLaOs) are uncommon conditions characterized by the occurrence of fragility fracture(s), most commonly vertebral, in late pregnancy or during the early postpartum period (O'Sullivan et al. 2006). The decrease in bone mineral density (BMD) during a physiological pregnancy can in rare cases be profound and may lead to dramatic microarchitectural changes, leading to increased incidence of spinal fractures (O'Sullivan et al. 2006). Information provided in the current literature on PLaOs is scant and it is focused mainly on the clinical description and management of isolated cases. In the current manuscript we aim to perform a narrative review of the available literature and highlight the clinical context of this rare entity. We performed an electronic search of the Pubmed/Medline database using the MeSH (Medical Subjected Headings) keywords "Pregnancy" and/or "Lactation" and "Osteoporosis" and "Human" that initially yielded 310 articles until September 2010. Further evaluation of the retrieved articles yielded 44 articles in English, most of which were case reports or case series; there was only one case control study of 35 women – the largest thus far (Dunne et al. 1993).

Calcium economy and bone physiology during pregnancy, postpartum and lactation

The developing fetal skeleton requires roughly about 30 g of calcium (80% of which are deposited in the third trimester of pregnancy) (Kovacs and Fuleihan 2006). Regarding changes in electrolyte levels of bone-supporting ions in the serum of the mother, ionized calcium and phosphorus remain normal (lower-than-normal total

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calcium i.e. ionized, complexed and albumin-bound calcium may be observed because of lower levels of albumin in pregnancy) (Cross et al. 1995; Dahlman et al. 1994;Gallacher et al. 1994). Intact parathormone (PTHi) decreases to low-normal levels in the beginning of pregnancy, due to mild suppression of parathyroid gland function, subsequently returning to pre-pregnant values (Rasmussen et al. 1990; Seki et al. 1991). PTH-related peptide (PTHrP, which is found during pregnancy in the placenta, desidua and amnion), in combination with increased levels of estradiol and prolactin, may be triggering factors for an increase in the action of renal 1-alpha-hydroxylase, since 1,25(OH)2 vitamin D levels during pregnancy are double the non-pregnant levels (intestinal calcium absorption also doubles and hypercalciuria ensues). (Kovacs and Kronenberg 1997). Serum markers of bone formation (osteocalcin, procollagen I carboxypeptides and bone-specific ALP) decrease during early pregnancy, rising up near term; urinary markers of bone resorption (pyridinoline and deoxypyridinoline, hydroxyproline) increase during pregnancy (Kovacs and Fuleihan 2006). The breast and the placenta produce calcitonin in pregnancy; subsequently its levels rise gradually throughout gestation (Woodrow et al. 2003). Beta hCG hypersecretion has been shown in osteolytic tumors; whether beta hCG can be implicated in pregnancy-induced bone loss is unknown (Rau et al. 2002).

In early pregnancy (as early as 8 weeks' gestation) changes in maternal bone structure have been observed: resorption cavities increase in size during early pregnancy, thus lowering bone volume. Bone volume recovers and osteoid increases as pregnancy evolves; nevertheless, overall BMD – albeit taking into account differences in assessment modalities and sites - may transiently decrease by 5 % (Purdie et al. 1988), returning eventually to prepregnancy levels (Ensom et al. 2002). Interestingly, the maternal loss of calcium during lactation for a duration of nine months is fourfold higher than during the nine months of pregnancy (Bowman and Miller 2001).

Hyper-, hypoparathyroidism and hypercalcemia in pregnancy

Primary hyperparathyroidism complicates 8/100,000 pregnancies per year (Heath et al. 1980) but may remain undetected, due to the decrease in total calcium and PTHi that is observed in normal pregnancies (of course an elevated ionized calcium in combination with a detectable PTHi should require further investigation). Weight loss, hyperemesis gravidarum or symptoms of preeclampsia may be manifest (Kelly 1991;Kort et al. 1999). Fetuses are at risk of neonatal tetany (due to suppression of the fetal parathyroids following maternal hypercalcemia); stillbirth or perinatal death are also grave complications. Treatment with hydration and correction of electrolyte disturbances and/or parathyroidectomy in the second trimester are advised for the mother. Neonates and infants benefit from calcium supplementation to correct hypocalcemia until 5 months post-partum (Shangold et al. 1982).

Hypoparathyroidism in pregnancy is rare and usually precedes conception. The increased need in pregnancy for calcium must not be neglected; calcium replacement/supplementation can protect the mother from hypocalcemia and the fetus from premature delivery and secondary hyperparathyroidism (Sadeghi-Nejad et al. 1980).

Inherited inactivating mutations of the calcium sensing receptor are the cause behind familial benign hypocalciuric hypercalcemia (FHH). This condition does not seem to alter bone metabolism: neither demineralization nor nephrolithiasis accompany it (Kovacs and Fuleihan 2006). Since it is an innate abnormality of calcium metabolism by the time pregnancy ensues, the affected mother's calcium metabolism has been "shifted" to a new equilibrium and no adverse effects on the fetus or herself have been recorded.

Pregnancy and lactation-associated osteoporosis (PLaOs)

In 1955 post-pregnancy osteoporosis was described for the first time (Nordin and Roper 1955); a few years later the first case of transient osteoporosis of the hip in pregnancy was also described (Curtiss and Kincaid 1959).

Pathophysiology. The extent of alterations in bone mineral content post partum and during lactation is variable, some reports show a decline in bone density while others show no change at all (Dunne et al.0 1993). The pathophysiology of PLaOs is still obscure. Although PLaOs may appear in previously normal skeletons of healthy women (Dunne et al. 1993), osteoporosis, osseous defects, bone undermineralization or an abnormal skeleton that preceded pregnancy may predispose to it (Dunne, et al. 1993). An unsuccessful first pregnancy has been shown to predispose to osteoporosis in a subsequent pregnancy (Khovidhunkit and Epstein 1996).

A pregnancy following one that was hampered with PLaOs is likely to be prone to PLaOs again; the longer the interval between pregnancies the more the woman is protected from PLaOs (Sowers et al. 1996). Prolonged and repeated lactation in a woman with PLaOs favors lower BMD and the reappearance of PLaOs in a future pregnancy (Dunne et al. 1993; Krebs et al. 1997). Children born of osteoporosis-related pregnancies have shown osteopenia in long term follow-up studies (Carbone et al. 1995). The maternal skeleton may be compromised by pregnancy prior to the attainment of peak bone mass; bone loss in teenage mothers may not recover as fast compared to bone loss in pregnancies of older females (Bowman and Miller 2001).

It has been argued that pregnancy elicits a biological stress that unmasks a defective maternal skeleton (Dunne et al. 1993). Inherited defects in collagen synthesis such as osteogenesis imperfecta, which is caused by mutations in the genes encoding for collagen type I (with a concomitant reduction of collagen synthesis by almost 50%), may be implicated in PLaOs (Weitzel and Percy 2000). There may be genetic predesposition to PLaOs: the mothers of some women with PLaOs had developed fractures at a young age (Dunne et al. 1993).

Low calcium and inadequate vitamin D levels may play a role. However, the intestinal absorption of calcium is increased during pregnancy, particularly after the second trimesters, and vitamin D levels are also increased (see above).

Vascular/neural causes of PLaOs have been proposed: femoral venous stasis secondary to compression by the gravid uterus (Longstreth et al. 1973), fetal pressure on the obturator nerve (this is debatable; human anatomy apparently does not favor this), marrow hypertrophy, immobilization, viral infection, trauma, and reflex sympathetic dystrophy (Kovacs 2001) and avascular necrosis (Hoffman and Kramer 1997).

Use of unfractionated heparin in pregnancy predisposes to osteoporosis (this has even been verified by transilial biopsy (Zimran et al. 1986)) via increase of osteoclast activity, inhibition of osteoblast activity and inhibition of calcification and mineralisation (caused by calcium ion binding) (Nelson-Piercy et al. 1997). However, use of low-molecular weight heparin was not associated with reduction in BMD (but fracture data have not been presented) (Le Templier and Rodger 2008).

Chronic therapy with corticosteroids, and anticonvulsants may cause secondary osteoporosis.

From studies in parathyroidectomized lactating rats it has been shown that PTH is not essential for mineral resorption and calcium mobilization during lactation (Bowman and Miller 2001). Nevertheless, breast-derived PTHrP may play a role in hypercalcemia, hyperclaciuria (Reid et al. 1992) and PLaOs, as shown in animal studies (VanHouten and Wysolmerski 2003) as well as in individual human cases (Reid et al. 1992; Sowers et al. 1996).

Diagnosis. PLaOs is encountered mostly in primigravidas (in the third decade of life) during the 3rd trimester (41 % of cases), or in early postpartum (56 %) (Khovidhunkit and Epstein 1996). The diagnosis of PLaOs is usually based on history, after exclusion of other underlying causes, and is supported by imaging findings of osteopenia and/or fragility fractures (Dunne et al. 1993). Fractures are mostly vertebral (thoracic or lumbar; fracture of the sacrum has been reported during pregnancy; it was attributed to vitamin D deficiency) (Breuil et al. 1997; O'Sullivan et al. 2006), while in a minority of patients, the hip is affected (transient osteoporosis of the hip) (Smith et al. 1995).

Symptoms of osteoporosis in pregnancy include pain in the lower thoracic or lumbar area, while hip PLaOs presents as unilateral or bilateral hip pain, limping, and possible hip fracture. BMD is diminished at the femoral neck and head, with increased water content in the bone and the marrow. In a published report, 24 of 56 patients with PLaOs had BMD measured; the average Z-score was -1.98 at the lumbar spine and -1.48 at the hip (Lakhanpal et al. 1987).

The differential diagnosis of PLaOs should include bone marrow edema, avascular necrosis of the hip or other inflammatory joint disorders. Pain lasts for 6-12 weeks and usually resolves within weeks (but may even take a year); BMD recovers within a year (Aynaci et al. 2008). In studies of women that suffered pain and/or vertebral collapse during pregnancy BMD was reported postpartum to eventually recover – particularly in the pain and/or fracture region - but up to a point, not reaching normal values (however, the studies are hampered by the fact that pre-pregnancy BMD scores were not assessed) (Phillips et al. 2000).

Treatment. No established treatment has been proposed for PLaOs. Mechanical measures, such as rest and avoidance of weight lifting are crucial, whereas supportive means for the spine (corset) may prove helpful. Exercise as well as extra supplementation with Vitamin D and calcium could cope for the losses and/or higher

requirements. Women that suffer pain or fractures during pregnancy should be discouraged from lactating, as this might aggravate the existing damage (Krebs et al. 1997). Regarding drug therapy, no adverse maternal and fetal outcomes from bisphosphonates' use before pregnancy and during the first trimester of pregnancy have been noted (Levy et al. 2009) and there are reports of bisphosphonates' use for PLaOs with good results vis-à-vis BMD (O'Sullivan et al. 2006); nevertheless this line of therapy remains controversial.

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