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Gestational osteoporosis: Myth or true?

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Abstract

Gestational osteoporosis is an existent rare clinical disease presenting with vertebral fractures and is quite often underdiagnosed. Etiology is heterogeneous and risk factors include family history of osteoporosis, low body mass index individuals, women with low physical activity, smoking, failure to achieve maximum bone mass and low level calories nutrition. In our review, we recorded the main hormones and biological markers involved in bone metabolism during pregnancy and breastfeeding period.

Regarding imaging methods, ultrasound and magnetic resonance are useful diagnostic tools and MRI can be used as a gold standard when examining hip pain in women who are in the third trimester of pregnancy. Available therapeutic approaches are recorded regarding conservative management and use of medication.

The implication of our work is to emphasize the importance of early identification of gestational osteoporosis. Medical specialties dealing with women during pregnancy and postpartum (obstetricians, endocrinologists, orthopedists) should assess the risk factors and be able to make the right diagnosis as early as possible for prognosis optimization.

Keywords: Gestational osteoporosis; Calcium homeostasis; Bone Metabolism Indices; Pregnancy calcium requirements

1. Introduction

Maternal calcium homeostasis is adjusted during pregnancy to meet these fetal requirements. Although the maximum calcium needs of the fetus appear in the third trimester (1), changes in maternal calcium metabolism start early in pregnancy. Physiological changes in elevated requirements comprise an increase in intestinal calcium intake, which is already doubling starting from the second quarter (2) and mainly an increase in the levels of 1,25 (OH)2 vit D (3). It should be noted that all of the above adjustments are made without an increase in PTH levels. (4)

Gestational osteoporosis is a relatively rare disease entity that is usually underdiagnosed. (5). It affects pregnant or postpartum women during breastfeeding, presenting significant morbidity (6). Risk factors include first-degree relatives of women with osteoporosis, low-weight individuals, women with low physical activity, smoking, failure to achieve maximum bone mass and poor nutrition. (7) Patients usually complain of severe pain in the lower lumbar spine during the third trimester of pregnancy or in the period immediately after childbirth due to vertebral fractures. (8) It is important that the medical specialties dealing with women during pregnancy and postpartum (gynecologists, endocrinologists, orthopedists) identify these patients early, identify the risk factors and be able to make the right diagnosis as early as possible.

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2. Literature review and modern perceptions

Both pregnancy and breastfeeding are normal conditions typically occurring in women <40 years of age. Studies show that during the first six months of lactation, about 4-6% of the total bone mass is lost due to the fall in estrogen and the loss of calcium because of breastfeeding (Lactation delays postpartum bone mineral accretion and temporarily alters its regional distribution in women.(9)

The increased calcium requirements during pregnancy and breastfeeding place women at an increased risk of developing osteoporosis. Although hormonal changes cause great calcium loss and increased bone resorption, the latter usually is reversed postpartum. This is why pregnancy and breastfeeding can have a double effect on bone density, which can be both beneficial and harmful. The end result is not readily predictable, and for this reason there is no absolute agreement on this issue. (10).

In order to better understand the pathophysiological mechanisms involved in bone metabolism during the pregnancy period, we will refer to the main hormones and indicators separately, for pregnancy and for the breastfeeding period respectively.

2.1. Gestational period

2.1.1. Inorganic ions

Hemoglobin and albumin levels decrease during pregnancy due to hemodilution. Because of these changes, total calcium appears to be much lower, sometimes even below normal levels. However, by making a correction for albumin, or measuring the calcium ion, we find that calcium remains at steady levels throughout pregnancy. The same applies to phosphorus and magnesium levels.(11)

2.1.2. PTH

Studies have found that during the first trimester of pregnancy PTH falls to the lowest normal levels and starts to rise from the middle of pregnancy to childbirth.(11)

2.1.3. Vitamin D

Levels of total calcitriol are doubled or tripled and remain elevated throughout pregnancy. On the other hand, free calcitriol is growing, mainly in the third trimester. PTH is usually the major stimulant of renal 1-hydroxylase. Pregnancy is an exception to the rule, as elevated levels of calcitriol occur when PTH is low. Data from studies show that it is not so much PTHrP, but other factors such as PTHrP, estradiol, prolactin and placental galactogen (hPL) that stimulate 1-hydroxylase activity.(12)

2.1.4. PTHrP

PTHrP is produced from various tissues in the fetus and mother and it is certainly unknown which of all sources is responsible for the large increase in maternal traffic. Because of the large increase in PTHrP, there is a corresponding increase in 1 hydroxylase, resulting in an increase in calcitriol and, indirectly, in the suppression of PTH. However, PTHrP is not as active as PTH in the stimulation of 1 hydroxylase in the kidney, so its contribution to increasing the calcitriol during pregnancy is still debatable. In in vitro studies it has been found that the C-terminus of PTHrP appears to inhibit bone resorption from osteoclasts and may play a protective role in the maternal skeleton during pregnancy. (13) (14)

2.1.5. Bone metabolism Indices

Bone metabolism indices (in serum or urine) have been systematically recorded during pregnancy. One major problem concerns their variability from person to person. During pregnancy additional problems are encountered in the adjustment of indices as they can usually not be evaluated due to lack of previous measurements due to hemodilution, increased GFR observed in pregnant women but also due to the placenta, uterus and embryonic skeleton itself. Bone absorption is assessed on the basis of catabolic products (deoxyproline, pyridinoline and hydroxyproline) in the urine, whereas new bone formation is based on serum indices (osteocalcin, C-terminal procollagen I peptide and ALP bone fraction) that are not normally affected by changes in GFR and haemodilution. Bone catabolism indices increase in the first weeks of pregnancy and until the middle of it, whereas bone growth indices, while initially low, have an increasing trend from mid-pregnancy to childbirth. It should be noted that overall ALP increases during pregnancy due to the placenta fraction and therefore it is not a reliable index of bone formation in this period.(15)

2.1.6. Intestinal calcium absorption

The intestinal calcium absorption increases significantly during the first 12 weeks of pregnancy and appears to be the most basic way of delivering calcium from the mother to the fetus. We now know that Vitamin D plays an important role in the intestinal absorption. However, observations have shown that the increase in microvilli calcium absorption during pregnancy occurs before the levels of calcitriol increase. It therefore appears that other factors other than vitamin D (such as placental galactogen, prolactin and so on) may stimulate intestinal absorption. Thus, it is not clear why, while the maximum needs of the fetus in calcium occur in the third quarter, absorption from the intestinal tract increases in the first quarter of pregnancy.(16) (17)

2.1.7. Renal calcium excretion

Renal clearance of calcium increases significantly during the first 12 weeks of gestation often at levels above normal, as a consequence of increased intestinal absorption. This is why the period of pregnancy is a risk factor for the appearance of kidney stones.(18) From the limited bone biopsies and the other hormonal and non-hormonal indices mentioned above it has been noted that bone resorption increases very early in pregnancy and reaches its maximum in the10th - 12th week of pregnancy. On the contrary, bone reshaping seems to be low, and sometimes normal. In any case, however, the overall difference is in favor of bone resorption in the first trimester. It is also noted that there is little calcium transfer from the mother to the fetus until the 12th week ,. Correspondingly, bone metabolism indices are low in the third trimester, when transplacental calcium transport from the mother to the fetus is at the highest point. All of this simply reinforces the view that skeleton of the pregnant woman plays a minimal role in calcium homeostasis and the main mechanism is through changes in intestinal absorption.(18)

Few studies have assessed bone marrow density (aBMD) due to possible exposure of the fetus (DPA was preferred to DEXA and qCT, to avoid the exposure of the fetus to radiation). In general, despite the prevailing view, there was no significant difference between cortical and spongy bone from pregnancy. Recent studies evaluated 16 women before pregnancy and immediately after the end of pregnancy using DEXA scan. In only a few of them a decrease in lumbar aBMD by 4-5% was found, one to six weeks postpartum. Whether this small decrease is true or due to the change in both the composition and the total body weight is not yet certain. However, it is certain that the postpartum period played an important role, since we know for sure that breastfeeding is always accompanied by bone loss at 1-3%. (19)

2.1.8. Osteoporosis in pregnancy

In 1959 Curtis and Kincaid were the first to describe the clinical and radiological entity of transient osteoporosis in the hip in three women who were in the last trimester of pregnancy, using the term: transient demineralization of the femoral head without the destruction of the knee joint.. Pregnancy is a dynamic condition that affects the female skeleton (especially during the third trimester) both mechanically and adaptively. It is known that this latter procedure is regulated by hormones and the response to hormones and to the needs of the fetus very rarely causes permanent, irreversible damage to the mothers. Osteoporosis in pregnancy is a very rare condition and its concrete pathophysiology remains unclear.

Osteoporosis in pregnancy usually occurs during the first pregnancy at 27-30 years of age. and is not related to the number of pregnancies. At a percentage of 60%, patients report pain in the lower lumbar spine.(20)

It is known that the mineralization of the embryonic skeleton is rapid in the third trimester of pregnancy and the necessary 33 grams required for the embryonic skeleton are complemented it in the third trimester, as it is then that the intestinal absorption of the mother through the action of 1,25 OH VIT D doubles . Gestation causes changes in both calcium and calciotropic hormone levels(21). During pregnancy, a moderate increase in bone turnover has been observed, and it is not certain whether significant changes in bone mass occur. In the lumbar spine, a small decrease in aBMD is observed, which is compensated for in long bones by intraosseous and periosteal deposition of bone tissue. During pregnancy, the intestinal calcium absorption in the mother increases, while during lactation it returns to normal levels, thus increasing the calcium requirements from the skeleton, to compensate for the increased needs associated with breastfeeding. The organism adjusts by increasing calcium absorption from the bones and reducing its renal clearance due to the increased production of PTHrP and the hypoestrogenic status resulting from high levels of prolactin. The reduction in bone mass, mainly seen in spongy parts of the bones, is restored within about 6 to 12 months after weaning. Parathyroid hormone-related protein (PTHrP) plays a key role in the process.(22). Gestational osteoporosis can manifest itself in the context of a chronic illness such as lupus erythematosus, Takayasu arteritis, Adamadiade-Behcet's disease, hypothyroidism, rheumatoid arthritis, psoriatic arthritis, Crohn's disease, and asthma (Dunne F, Walters B, Mashall T, Health DA.Pregnancy associated osteoporosis. 39, 487-490). Potentially underlying genetic causes should be considered when examining pregnancy-related osteoporosis (23)

Lastly, in several studies of the past, heparin-induced osteoporosis has been reported during pregnancy. Heparin in combination with aspirin increases the rates of birth of living babies in pregnant women with repetitive miscarriages and antiphospholipid syndrome. This disease entity was first described in 1965 by Griffith (24). However, pregnant women requiring prophylactic administration of LMWH or heparin receive sufficient amounts of calcium and vitamin D (25)

It is not possible to predict which women will have gestational osteoporosis because of the many confusing factors mentioned above. However, if we want to find a prognostic index, we could simply look for retrospective evidence that shows low BMD and low-force fractures - which are characterized by low sensitivity and specialty(26).

2.2. Breastfeeding period

As we enter breastfeeding, the needs for calcium change. Daily losses due to milk rise to 210 mg and sometimes even to 1000 mg when nursing twins. Unlike the gestational age where women meet their daily calcium requirements, mainly by increasing intestinal epithelium absorption, in lactation we find different mechanisms of balancing trace elements.

2.2.1. Inorganic ions

The levels of albumin-corrected Ca and ionized Ca are normal. This is not the case with phosphorus, which is found at higher than normal levels. The increased rate of phosphorus from the diet, combined with that resulting from the degradation of the mother's skeleton, and the reduction in renal ion excretion, comprise the main mechanism that increases phosphate in the serum during breastfeeding.(26)

2.2.2. PTH

During the first few months of lactation, PTH levels may range from zero to 50% of normal. It comes to normal after weaning, and in some cases there is a slight increase above the normal limit (27)

2.2.3. Vitamin D

Not only during pregnancy, but also during breastfeeding there is always the fear of exhaustion of 25KV vitD maternal levels because of the needs of the fetus as well as the placental activity. However, in observational and in several retrospective clinical studies, in particular on the placebo side, it has been found that during breastfeeding, even in women with very low levels of vitamin D, no significant change was observed in the amount of 25OH vitD, or the decrease observed was non-statistically significant. Generally, while in pregnancy the calcitriol levels were twice the normal ones, they immediately fall into the normal range and remain there throughout breastfeeding. (28)

2.2.4. PTHrP

PTHrP levels are significantly higher in women who are breastfeeding than in non-pregnant women. It seems that the source of PTHrP is the mass gland that secretes PTHrP into breast milk at concentrations 10,000 times higher than those observed in patients with tumor-induced hypercalcemia. The particular correlation of PTHrP with the mass gland is also shown by studies showing that this hormone is an important factor in the development of the breast itself and in its adequate blood flow, as well as in determining the composition of breast milk, as it is involved in the process, and of the amount of water and the amount of calcium present therein. (29) .

During lactation, PTHrP is induced in the mother's circulation through the mass gland, resulting in increased bone resorption, increased renal tubular calcium reabsorption and indirectly decreased PTH levels. (30).

Intestinal calcium absorption While during pregnancy there was an increased calcium absorption from the intestinal villus, immediately after birth we found a rapid decrease in absorbability to levels similar to those of non-pregnant women.

2.2.5. Renal calcium elimination

Renal calcium excretion during breast-feeding is significantly reduced to approximately 50 mg per 24 hours, and the overall renal clearance is also reduced. These findings support the view that renal calcium reabsorption is greatly increased mainly through the action of PTHrP.(31)

2.2.6. Bone Metabolism of Calcium and Bone Density - Bone Metabolism Indices

From histomorphometric data in mice it was found that about 2-3% of bone minerals are lost in the first 2-3 weeks of breastfeeding. For obvious reasons, corresponding data are not present in humans. However, in various studies it has been noted that bone mineral absorption indices appear to increase 2-3 times during breast-feeding, and are found to be significantly higher than in the third trimester of pregnancy. Bone reconstruction indices in the serum are also increased, but compared to the bone resorption indices they are lower.(32)

Repeated aBMD measurements during breastfeeding have shown that the inorganic 'store' of the mother's bone loses 3 to 10% of its efficacy after 6 months of breastfeeding, mainly in spongy bones. This loss has a rate of 1 - 3% per month, is an adjunct to lactation and cannot be prevented however much calcium is give through nutrition.(33)

In addition, low levels of estrogens during breastfeeding also play an important role in the process of bone resorption. However, the previous bone loss is not as big as imagined. Suffice it to think that in women receiving GnRH agonists for endometrial therapy while their estrogen levels are much lower than those found in breastfeeding, bone loss in spongy bones is only 1-4% after 6 months of treatment and in every case it is much lower compared to bone loss in breastfeeding. The difference is precisely due to the effect of PTHrP that works complementarily to the action of estrogen stimulating osteoclasts and increases renal calcium reabsorption. (34).

The bone mass is reduced and eventually reversed completely 6 - 12 months after weaning. This corresponds to a bone density gain of about 0.5 - 2% / month. The exact bone reconstruction mechanism is not yet completely clear. Studies in rats show that it is probably not due to the levels of calcitriol, calcitonin, PTH or PTHrP, nor can it be fully explained by the recovery of estrogen levels. Overall, most studies have found no correlation of breastfeeding history with peak bone mass, bone density, and hip fracture risk. That is why we can say that the loss of bone structure due to breastfeeding does not pose a serious clinical risk to the woman. (35)

Bone loss may be important since even minimal force can cause a fracture.(36) , although retrospective epidemiological studies involving a general population of premenopausal women and postmenopausal women have shown that pregnancy is not associated with increased cognitive risk (37) (38)

Osteoporosis after pregnancy can lead to vertebral fractures, height loss, back pain, and fractures in other anatomical sites. In total, only about 120 incidents involving osteoporotic fractures during pregnancy have been reported (39) with the largest recorded series listing 35 cases (40)

Pre-existing low bone density and high rate of bone turnover during pregnancy and lactation can play an important role. Generally speaking, however, the clinical image of osteoporosis does not differ from the classical image of osteoporosis, since it appears after delivery (2/3 of cases) and only in 1/3 of cases during the third trimester (very rarely in childbirth) and 70% of these cases occur in the first pregnancy (although the symptoms can be observed in the second pregnancy at a 23% rate and even more rarely in the third pregnancy at a 7% rate. (41) (42).

The most common symptom is spine pain, mainly at the lower thoracic level, which may reduce the mobility of the woman, while the loss of height along with possible predisposing kyphosis will show in multiple vertebral fracture localizations. A precursor symptom may be the pain during the walking process (antalgic gait).

We should specifically refer to the clinical picture of osteoporosis of the hip, in which the onset of the pain is sudden, keeping the wide trajectory of the movements (except extreme positions mainly on the rotors), while in the osteonecrosis of the hip there is a progressive increase of the pain with reduction of the wide motion of the joint (43)

2.2.7. Imaging Control

It is logical, with respect to imaging control, that ultrasound and magnetic resonance imaging be allowed during pregnancy, and it is the magnetic resonance imaging that can diagnose gestation osteoporosis, if there is extensive edema in the area (44), which is the most common cause of osteoporosis in pregnancy, and is proposed as the chosen method when examining hip pain in women who are in the third trimester of pregnancy (45). Performing magnetic resonance imaging is deemed even more urgent because it is even more difficult for gestation osteoporosis and osteonecrosis to be diagnosed when there are pre-existing factors for osteonecrosis such as alcohol, steroid, renal failure or chemotherapy (43) (46)

Postpartum extensive imaging control of the bone mass of the vertebral column and the hip should be performed. The finding of low bone mass of the spine should be accompanied by simple x-ray of thoracic and lumbar spine to detect

possible bifocal or wedge-shaped deformations. Similarly, the low bone mass in the region of the hip (the whole hip or neck hip) should be accompanied by imaging control of the hip to exclude a hypometric hip fracture MRI (47)(48), however, apart from being a diagnostic tool, is also suggested for monitoring the progression of the disease.(49) The bone biopsy is not necessary and will show a picture compatible with osteoblastic insufficiency, thus confirming the diagnosis of osteoporosis without an osteomalacia image session (50) (51) (52).

2.2.8. Conservative treatment

It is particularly important to document the diagnosis and exclude all other cases with a clinical image similar to that of gestational osteoporosis. Solomon argues that the difference between bone marrow edema associated with aseptic necrosis and that without aseptic necrosis should be recognized as a self-limiting entity (53).

The majority of symptoms can be treated with conservative treatment, without a specific diagnosis, so many cases are under-diagnosed. The presence of a persistent pain in the hip or lumbar spine, antalgic gait, height loss, and kyphosis, will require the treating physician to see the possible presence of osteoporotic fractures. The typical treatment involves the addition of calcium and vit D supplements, a treatment that can increase bone mineral density in the lumbar spine by 6.2% in 8-18 months, and by 4.1% in the hip respectively (54).

The avoidance of strain is considered necessary to avoid fracturing the hip or the thoracolumbar spine, consequently the avoidance of normal deliveries, since this posture increases the risk of a hip fracture. Forbidding postnatal breastfeeding is probably the most effective measure to reduce the loss of bone mineral density (55).

Although the literature is poor, there are studies that support the therapeutic use of bisphosphonates or teriparatide(56)(57)(58).

The effects of bisphosphonates during pregnancy on the embryo are based on animal studies and have shown that these drugs pass through the placenta and it is likely that the administration of such pharmaceutical preparations is a mispractice (59) (60).

However, studies have also been conducted using bisphosphonates, the therapeutic effects of which were satisfactory and safe (61).

After BPs administration, O-Sullivan et al in 2006 argued that the BMD of the spine increased by 17% and 23% in one and two years respectively and the BMD in the hip increased by just 0.7% in 1 year and not at all in 2 years of treatment (62). Thus, the use of Ibandronate, clodronate, pamidronate, neridronate, alendronate in combination with calcium and vitamin D has occasionally been suggested.(63)(64)(65)(66)(67).

Even more rarely, the use of intravenous bisphosphonates or zoledronic acid (68)**,** either pamidronate (69) or ibandronate has been suggested (70).

Recently, the use of denosumab has also been suggested, with satisfactory results(71) In one of the two patients in the study, kyphoplasty was initially performed, following immediate post-operative treatment with denosumab, and her bone strength was confirmed through HR-pQCT.

The therapeutic use of the teriparatide has occasionally been bibliographically supported.(57). The anabolic character of this drug that binds to bone resistance and has a lifespan of 0.5 - 1 hour is a better therapeutic approach to gestation osteoporosis, (72) which proves to be true since this pharmaceutical agent proves to act and immediately relieve vertebral fracture pain (73).

In clinical cases Lampropoylou-Adamidou et al after 13 months of PTH administration reported that BMD increased by 24.4% in the CR, 9.9% and 4.6% in the left and right hip, and 12.6% and 7.8% in the left and right femoral thighs without the occurrence of new fracture at this time (74). Similarly, there are other studies with similar increases in BMD ***(***75***)*** ***(***76) (77).

Even fewer studies suggest that in case the conservative treatment fails surgical treatment would be appropriate, either in the form of osteosynthesis, or arthroplasty, or transdermal vertebroplasty or predominantly kyphoplasty (78)(79)(80)(81)***.***

Especially in the case of vertebroplasty, it is preferable to use calcium phosphate as a bioabsorbable material as compared to conventional polymethylmethacrylate (82).

Some researchers support the simultaneous use of kyphoplasty and drug therapy, or the use of kyphoplasty and a halo, or modern kyphoplasty and spray calcitonin (83)(84)(85).

The prognosis is generally good as symptoms are improved at a rapid rate postpartum (86) (87) (88).

Ever since 2000 it has been demonstrated that even just Calcium and Vit D administration can increase the BMD of the spine by 6.2% over 8-18 months and by 9.5 % over 4.2 years, with a corresponding increase in BMD of the hip during the same time periods by 4.1% and 4.4% respectively(89) .

Along with this study , another study in 28 women that was conducted during the same time period, confirmed that bone density returns to preterm pregnancy rates after about 4 years and estimated that during this time span the overall lactation time (i.e. the interval between weaning and subsequent pregnancy) plays the key role (90). Subsequent reports support the above findings and suggest steady supply of vit D and calcium (91).

3. Conclusion

Gestational osteoporosis fortunately is a rare clinical feature and presents a heterogeneity in etiology and prognosis. It typically occurs with vertebral fractures in the first trimester of pregnancy or immediately after childbirth. It is rarely repeated in the next pregnancies if secondary etiology is found and treated. It is partially restored after some years, in women without secondary causes who have not been treated. The assessment of bone mass and biochemical indices of bone resorption and bone reconstruction during labor is generally considered to be a risky factor, as, firstly, it is difficult to distinguish pathological from normal BMD and secondly the biochemical indices are affected by many confounding parameters at this stage. Additional studies should be conducted to crystallize the overall changes occurring during pregnancy and lactation.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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