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## ENDOCRINOLOGY IN PREGNANCY AND OSTEOPAROSIS

**Abstract**

Pregnancy defines a challenging period to the mother's bones because the building of the fetal skeleton requires a substantial transfer of calcium. This process is particularly intense during the third trimester, when fetal bones experience substantial growth and calcification. The regulatory mechanisms are still poorly understood, but it seems patent that the drainage of calcium from the mother has to bear some level of deterioration of the maternal skeleton unless compensatory mechanisms of enough potency are at play. If an adequate balance is not achieved, pregnancy would define a vulnerability period for maternal bones. Osteoporosis or even fragility fractures might be conceived whether the decalcifying process is particularly intense or whether there is an osteopenic background. In fact, isolated cases of osteoporosis or fragility fractures have been described in the literature (1, 2). However, the process has to be transitory, because pregnancy has not been detected as a risk factor for postmenopausal osteoporosis.

***Key words**: pregnancy, postmenopausal osteoporosis, bone destroying, vitamin D, osteopenic, osteocytes*

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## Hamiləlikdə endokrinologiya və osteoparoz

**Xülasə**

Hamiləlik zamanı qadının sümükləri üçün çətin bir dövr başlayır, çünki dölün skeletinin qurulması kalsiumun əhəmiyyətli bir transferini tələb edir. Şəkərli diabetli xəstələrdə sümük metobalizmasında dəyişikliklər qacılmazdır.Məqalədə hamiləlik zamanı və həmcinin şəkərli diabetde sümük dəyişiklikləri əsaslı araşdırılıb. Bu proses xüsusilə üçüncü trimestrdə, fetal sümüklərin əhəmiyyətli dərəcədə böyüməsi və kalsifikasiyası ilə qarşılaşdıqda intensiv olur. Əgər adekvat tarazlıq əldə olunmazsa, hamiləlik ana sümükləri üçün həssaslıq dövrünü təyin edər. Osteoporoz və ya hətta kövrəklik sınıqları, kalsifikasiya prosesinin xüsusilə intensiv olub-olmamasından və ya osteopenik fonun olub-olmamasından asılı olmayaraq düşünülə bilər. Əslində, ədəbiyyatda osteoporoz və ya kövrəklik

sınıqlarının təcrid olunmuş halları təsvir edilmişdir (1, 2). Bununla belə, proses keçici olmalıdır, çünki hamiləlik postmenopozal osteoporoz üçün risk faktoru kimi aşkar edilməmişdir.
***Açar sözlər:*** *hamiləlik, postmenopozal osteoporoz, sümüklərin zədələnməsi, D vitamini, osteopenik, osteositlər*

## İntroduction

Data from studies on bone metabolic changes during pregnancy were collected from experimental and clinical papers. Case reports or case series on women who were diagnosed of densitometric osteoporosis during pregnancy were considered eligible irrespective of whether a fragility fracture had occurred. The main objective of calcium adjustments during pregnancy is to enable the adequate transplacental transfer of ∼30g of calcium required for the successful mineralization of the fetal skeleton. Eighty percent of that amount is transferred during the third trimester, when placental calcium transport averages 110–120mg/kg per day (4). The fetus enjoys a status of persistent hypercalcemia, where a calcium placental pump maintains a gradient irrespective of the calcium status in the mother. This means that insufficiencies in the adjusting machinery in the mother will entail decalcification at her skeleton, something that may be a universal phenomenon at the third trimester, when the transfer of calcium increases drastically.

The concentration of 1–25 (OH)2 vitamin D3 (calcitriol), the active metabolite of vitamin D, increases during pregnancy. The increase, already detected at the first trimester, continues up to term, when it attains levels that are several fold higher than before pregnancy (5, 6). Maternal kidney, and possibly placenta, decidua, and fetal kidney, provide the necessary 1α-hydroxylase activity. The contribution of the extra-renal sources, however, seems to be of little significance, as suggested by the inappreciable changes in calcitriol reported in an anephric woman during pregnancy (7).

The changes in vitamin D are concomitant with the improvement in the efficiency of the intestinal absorption of calcium, which doubles its capacity. This intestinal adaptation seems to be important in helping the mother to accommodate the fetal demand for calcium. It may be speculated, therefore, that further increases in the levels of vitamin D might translate into a more efficient calcium transfer at the intestine. The point is of interest, because the prevalence of vitamin D insufficiency, including the population of pregnant women, is elevated (8), even in low-latitude countries, where sun exposure is high (9). In this context, it may be conceived that a potential role exists for vitamin D analogs, as these compounds are designed to increase the effects of vitamin D while minimizing pathological hypercalcemia (10). Moreover, these analogs might escape from the limiting factor represented by the increase in vitamin D-binding protein (DBP (GC)), which, as in other high-estrogen states, increases during pregnancy (11). This hypothesis, however, has not been tested.

DBP deserves attention in pregnancy because, together with its role as the major binding protein for 25(OH) vitamin D and calcitriol, it may act as an actin scavenger, bind fatty acids, and modulate immune and inflammatory responses (12). Moreover, DBP may be found not only in serum, but also in other biological fluids. The detection in cervicovaginal fluid (13), for example, has been taken to propose DBP as an indicator of up-regulated cell death and tissue remodeling accompanying labor (14).

The role of vitamin D in the modulation of the increased intestinal transport of calcium should still be clarified. Experiments with pregnant vitamin D-deficient rats and vitamin D receptor-null mice have shown that the increase in calcium absorption was similar to controls (15). Interestingly, recent experimental data in mice indicate that maternal hypervitaminosis D may actually reduce fetal bone mass and mineral acquisition (16).

However, it is now known that hypocalcemia derives from the physiological hypoalbuminemia of pregnancy, which coexists with unaltered levels of free calcium, the real reset regulator of PTH levels (17). Moreover, there is no change in phosphate levels, and more reliable immunoassays, either immunoradiometry with the use of a double-antibody technique or electrochemiluminescence, confirm that the circulating PTH level slightly decreases during pregnancy and normalizes at the end of this state (18). Murine models further exclude the participation of the hormone in the increase in calcitriol level during pregnancy or the recovery of bone mass after lactation (19).

Pregnancy also involves changes in the circulating levels of IGF1. The oscillations are small during the first and second trimesters, but then the peptide increases during the third trimester and decreases

*post partum* (18, 22, 29). These changes seem to be influenced by active participation of PGH, which gradually replaces the control in the synthesis of IGF1 during the second half of pregnancy (30).

PGH, which should be distinguished from placental lactogen (HPL), is the product of the expression of the *GHV* (*GH2*) gene, as opposed to pituitary GH, which is the product of the *GHN* (*GH1*) gene (30). PGH is secreted in the syncytiotrophoblast from the 6th week of pregnancy and gradually replaces pituitary GH during pregnancy (20, 22). PGH is found only in maternal blood and is supposed to influence the availability of nutrients to the placenta. A prospective clinical study found a significant association between PGH and fetal growth during normal pregnancy (29). This modulation may be direct, by autocrine or paracrine mechanisms, or indirect, by regulation of IGF1 (28).

The participation of osteoblasts and osteocytes as active regulators of bone homeostasis has been shown in studies conducted in animal models and in the human. The case of osteocytes is of particular interest because, contrary to past concepts, they have manifested as multifunctional cells with crucial regulatory roles in several mechanisms affecting bone homeostasis (30). Among their abilities, osteocytes may remove and replace their perilacunar matrix, a concept baptized as 'perilacunar remodeling', which has been shown to be regulated by hormonal changes in mice. Lactation, for example, is associated with increases in osteocyte lacunar area. The potential participation of this mechanism in the maternal and fetal bone changes during pregnancy is still obscure (29). There is still sparse information on the possible implication of the Wnt pathway in the development of the fetal skeleton (21). A recent Scandinavian study has found that the circulating levels of sclerostin were lower in the mother at the 30–32 weeks of pregnancy than in the umbilical cord at delivery (24). Interestingly, cord sclerostin, but not maternal sclerostin, was significantly associated with dual-energy X-ray absorptiometry (DXA)-measured total body bone mineral content (BMC) in the newborn. The levels of FGF23 and of α-klotho, the FGF23 obligatory co-receptor, were measured in the same study. While the levels of FGF23 were similar in the maternal and the fetal compartment, those of α-klotho were higher in the umbilical cord plasma.

Estrogens are known down-regulators of bone resorption , and therefore, should act to contain the accelerated loss of bone mass. There is no indication suggesting an alternative role for estrogens during pregnancy. The case of PRL is more complicated (22). Data from experimental studies have shown that there are PRL receptors in human osteoblasts and that their activation leads to reduced proliferation and mineralization potential of these cells . Moreover, studies on rats have shown that PRL directly stimulates osteoblasts to increase the ratio of RANKL to OPG. The limiting action of OPG on the pro-resorptive potential of RANKL would translate into increased loss of bone mass (26).

The overall effect of pregnancy on the skeleton has been investigated by methods that include histology, imaging techniques, and BBMs. Before describing the findings observed with each approach, it is important to stress that, whichever the derangement of bone metabolism during pregnancy, it seems that there is no carryover effect. This is so even considering that the deterioration of bone density accelerates during lactation, when maternal bone is the main source of the considerable amounts of calcium provided with breast milk (17). However, the rapid loss in bone mineral density (BMD) during lactation, which may attain 5–10% in 2–6 months, restores along the 6–12 months after weaning through still unclear mechanisms . This fast recovery is reflected in epidemiological studies, which do not find an association between the number of pregnancies or the duration of lactation and the future diagnoses of either osteoporosis or fragility fracture (29).

Both techniques may be used because the low irradiation does not affect fetal safety and even less at the advanced stage of gestation in which the problem arises. However, the low incidence of this pathology does not support the generalized use of DXA for screening unless there are clear risk factors, which have not been described. Consequently, it is only the good clinical judgment as a consequence of abnormally increased pain at either the back or the joint, which should raise the suspect of a fracture (27).

The irradiation dose absolutely limits the use of computed tomography, but interest is arising on the use of alternative technologies, such as magnetic resonance (MR), which can be safely used during pregnancy. MR may be particularly efficacious in detecting vertebral fractures, which may be missed by conventional radiography . Moreover, MR may help in the diagnosis of the regional forms, because the accompanying bone marrow edema may be detected by this technology. Located at the epiphysis and extending into the subcondral bone, edema is often accompanied by joint effusion .

## References

1. Khovidhunkit W, Epstein S. Osteoporosis in pregnancy. *Osteoporosis International* 1996 6 345–354.
2. Smith R, Athanasou NA, Ostlere SJ, Vipond SE. Pregnancy-associated osteoporosis. *Quarterly Journal of Medicine* 1995 88 865–878.
3. Atkins D, Best D, Briss PA, Eccles M, Falck Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D et al.. Grading quality of evidence and strength of recommendations. *BMJ* 2004 328 1490.
4. Kovacs CS. The role of vitamin D in pregnancy and lactation: insights from animal models and clinical studies. *Annual Review of Nutrition* 2012 32 97–123.
5. Cross NA, Hillman LS, Allen SH, Krause GF, Vieira NE. Calcium homeostasis and bone metabolism during pregnancy, lactation, and postweaning: a longitudinal study. *American Journal of Clinical Nutrition* 1995 61 514–523.
6. Ritchie LD, Fung EB, Halloran BP, Turnlund JR, Van Loan MD, Cann CE, King JC. A longitudinal study of calcium homeostasis during human pregnancy and lactation and after resumption of menses. *American Journal of Clinical Nutrition* 1998 67 693–701.
7. Turner M, Barré PE, Benjamin A, Goltzman D, Gascon-Barré M. Does the maternal kidney contribute to the increased circulating 1,25-dihydroxyvitamin D concentrations during pregnancy? *Mineral and Electrolyte Metabolism* 1988 14 246–252.
8. Holick MF. Vitamin D deficiency. *New England Journal of Medicine* 2007 357 266–281.
9. Karras SN, Anagnostis P, Annweiler C, Naughton DP, Petroczi A, Bili E, Harizopoulou V, Tarlatzis BC, Persinaki A, Papadopoulou F et al.. Maternal vitamin D status during pregnancy: the Mediterranean reality. *European Journal of Clinical Nutrition* 2014 68 864–869.
10. Leyssens C, Verlinden L, Verstuyf A. The future of vitamin D analogs. *Frontiers in Physiology* 2014 5 122.
11. Bikle DD, Gee E, Halloran B, Haddad JG. Free 1,25-dihydroxyvitamin D levels in serum from normal subjects, pregnant subjects, and subjects with liver disease. *Journal of Clinical Investigation* 1984 74 1966–1971.
12. Gomme PT, Bertolini J. Therapeutic potential of vitamin D-binding protein. *Trends in Biotechnology* 2004 22 340–345.
13. Dasari S, Pereira L, Reddy AP, Michaels JE, Lu X, Jacob T, Thomas A, Rodland M, Roberts CT Jr, Gravett MG et al.. Comprehensive proteomic analysis of human cervical-vaginal fluid. *Journal of Proteome Research* 2007 6 1258–1268. 14.Liong S, Di Quinzio MK, Fleming G, Permezel M, Georgiou HM. Is vitamin D binding protein a novel predictor of labour? *PLoS ONE* 2013 8 e76490.
14. Fudge NJ, Woodrow JP, Kovacs CS. Pregnancy rescues low bone mass and normalizes intestinal calcium absorption in Vdr null mice. *Journal of Bone and Mineral Research* 2006 21 (Suppl) S52.
15. Lieben L, Stockmans I, Moermans K, Carmeliet G. Maternal hypervitaminosis D reduces fetal bone mass and mineral acquisition and leads to neonatal lethality. *Bone* 2013 57 123–131.
16. Kovacs CS. Calcium and bone metabolism disorders during pregnancy and lactation. *Endocrinology and Metabolism Clinics of North America* 2011 40 795–826.
17. Moller UK, Streym S, Mosekilde L, Heickendorff L, Flyvbjerg A, Frystyk J, Jensen LT, Rejnmark L. Changes in calcitropic hormones, bone markers and insulin-like growth factor I (IGF-I) during pregnancy and *postpartum*: a controlled cohort study. *Osteoporosis International* 2013 24 1307–1320.
18. Kirby BJ, Ma Y, Martin HM, Favaro KL, Karaplis AC, Kovacs CS. Upregulation of calcitriol during pregnancy and skeletal recovery after lactation do not require parathyroid hormone. *Journal of Bone and Mineral Research* 2013 28 1987–2000.
19. Ardawi MS, Nasrat HA, BA'Aqueel HS. Calcium regulating hormones and parathyroid hormone-related peptide in normal human pregnancy and *postpartum*: a longitudinal study. *European Journal of Endocrinology* 1997 137 402–409.
20. Hirota Y, Anai T, Miyakawa I. Parathyroid hormone-related protein levels in maternal and cord blood. *American Journal of Obstetrics and Gynecology* 1997 177 702–706.

21. Black AJ, Topping J, Durham B, Farquharson RG, Fraser WD. A detailed assessment of alterations in bone turnover, calcium homeostasis, and bone density in normal pregnancy. *Journal of Bone and Mineral Research* 2000 15 557–563. 23.Wysolmerski JJ. Parathyroid hormone-related protein: an update. *Journal of Clinical Endocrinology and Metabolism* 2012 97 2947–2956.
22. Care AD, Abbas SK, Pickard DW, Barri M, Drinkhill M, Findlay JB, White IR, Caple IW. Stimulation of ovine placental transport of calcium and magnesium by mid-molecule fragments of human parathyroid hormone-related protein. *Experimental Physiology* 1990 75 605–608.
23. Sato K. Hypercalcemia during pregnancy, puerperium, and lactation: review and a case report of hypercalcemic crisis after delivery due to excessive production of PTH-related protein (PTHrP) without malignancy (humoral hypercalcemia of pregnancy). *Endocrine Journal* 2008 55 959–966.
24. Riccardi D, Brennan SC, Chang W. The extracellular calcium-sensing receptor, CaSR, in fetal development. *Best Practice & Research. Clinical Endocrinology & Metabolism* 2013 27 443–453.
25. Kovacs CS, Lanske B, Hunzelman JL, Guo J, Karaplis AC, Kronenberg HM. Parathyroid hormone-related peptide (PTHrP) regulates fetal–placental calcium transport through a receptor distinct from the PTH/PTHrP receptor. *PNAS* 1996 93 15233–15238.
26. Simmonds CS, Karsenty G, Karaplis AC, Kovacs CS. Parathyroid hormone regulates fetal–placental mineral homeostasis. *Journal of Bone and Mineral Research* 2010 25 594–605.
27. Chellakooty M, Vangsgaard K, Larsen T, Scheike T, Falck-Larsen J, Legarth J, Andersson AM, Main KM, Skakkebaek NE, Juul A. A longitudinal study of intrauterine growth and the placental growth hormone (GH)–insulin-like growth factor I axis in maternal circulation: association between placental GH and fetal growth. *Journal of Clinical Endocrinology and Metabolism* 2004 89 384–391.
28. Lacroix MC, Guibourdenche J, Frendo JL, Muller F, Evain-Brion D. Human placental growth hormone – a review. *Placenta* 2002 23 (Suppl A) S87–S94.

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