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Original Research

Do bone turnover markers change with a steep drop in maternal steroids?

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Summary

Objectives: To study the changes of bone physiology during last trimester and compare it with immediate postpartum period associated with the sharp drop of pregnancy steroids. *Introduction:* The maximum transport of calcium and phosphate is at 36 weeks. The sudden drop of sex steroids after delivery could probably lead to a significant change in bone turnover markers. This study was performed to demonstrate if this has an impact on bone turnover markers (BTM). *Materials and Methods:* Women with a singleton non-complicated pregnancy were recruited from July 29, 2010 for two months to the end of September 2010. A serum level of bone profile, 25 OH vitamin D, and BTM was taken at 35-36 weeks and repeated at postpartum. A paired *t*-test using SPSS 16 was used to compare the means. *Results:* Serum bone profile values were comparable between the two groups. Although the mean postpartum serum value of 25-Oh vitamin (28.06 nmol/L) was lower than during pregnancy (35.72 nmol), it did not reach a statistical significance, in this population. A trend of increase in serum osteocalcin postpartum was observed ($p = 0.05$). *Conclusions:* This group of women had a high prevalence of vitamin D deficiency; this was not accompanied with changes in BTM; this suggests that a change in the level of steroids play a role that modify the expected interaction between vitamin D and BTM. Larger studies are however needed.

Key words: Bone mineral density; Sex steroids; Vitamin D; Bone turnover markers.

Introduction

The pregnant woman's body provides 25 to 30 grams of calcium to support the developing fetal skeleton. Much of the fetal calcium demand occurs in the third trimester of pregnancy, Calcium homeostasis is achieved through dietary intake, intestinal absorption, skeletal accretion and resorption, and urinary excretion. The key organs involved in the changes in calcium metabolism during pregnancy include the maternal parathyroid gland, the maternal intestine, and the feto-placental unit. An increase in 1, 25-dihydroxyvitamin D, derived primarily from the placenta, stimulates intestinal absorption of calcium and phosphate, and appears to be the key regulatory factor during pregnancy [1]

Serum concentrations of collagen crosslinks reflect bone resorption but not dietary intake, and these make them better indicators of bone resorption than urinary calcium or hydroxyproline excretion [2]. The c-telopeptide crosslink (CTX) was used in this study.

During early pregnancy, levels of osteocalcin (a marker of new bone formation) decline, reaching a nadir at mid-gestation, and then rise to pre-pregnancy levels by term [3-5]. This pattern is similar to the changes in parathormone (PTH) levels during pregnancy (initial decline followed by a rise) and indicates a progressive decrease and then increase in bone turnover during pregnancy [3, 6].

The overall controlling factors involved in bone homeostasis during pregnancy are yet unknown.

A recent two-year study demonstrated a 2% decrease of bone mineral density of 59 pregnant and lactating women by using ultra-distal radius bone mineral density, suggesting that maternal skeleton may be an important source of calcium transported to the fetus [6].

Although dual-energy absorptiometry (DXA) is far superior for the diagnosis of osteoporosis**,** bone turnover markers (BTM) give some indication about the future risk for bone loss and fractures. Several assays are currently available that measure BTMs, (7). These assays measure collagen breakdown products released from osteoclasts and osteoblasts during the process of bone resorption and formation.

This study was performed to compare the serum level of bone turnover markers (osteocalcin and CTx) at 35-36 weeks (the maximum time of a change) and postpartum level, when pregnancy steroids levels drop considerably.

Materials and Methods

Thirty-five women were recruited for the study. These women were followed at King Abdulaziz University Hospital. During their visit at 35-36 weeks, they had a blood sample for 25- OH vitamin D, PTH, bone profile including serum calcium, phosphate and alkaline phosphatase, and thyroid function tests, and BTMs. The same tests were repeated first day postpartum during their

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hospital stay.

Vitamin D was tested using automated based on electrochemiluminescence (ECL) technique, with normal values being 75-200 nmol/ml. BTMs were tested using (enzyme linked immunosorbent assay (ELISA), manual technique with calibration or validation with normal controls. The normal values for these bone turnover markers were, osteocalcin: 4-15 ng/ml and CTx: 0.1-1.27 ng/ ml (as per manufacturer). A comparison was made between the values of these tests at these time intervals using a paired *t*-test using SPSS 16.

Results

The bone profiles done at 36 weeks and postpartum were compared. There was no significant statistical difference between the two groups. The mean serum value of 25-OH vitamin during pregnancy, was low in this population (35.72 nmol/l), one women only had a normal level (75-200 nmol/l) while all others had moderate (< 25-50 nmol/l) or severe (< 12.5-25 nmol/l) vitamin D deficiency. The mean postpartum level was 28.06 nmol/l and one only within normal. Comparing the two means with paired *t*- test revealed no significant difference. The mean serum level of osteocalcin at 36 weeks and postpartum showed a trend to increase (14.1 and 16.49 ng/ml, respectively) with a $p = 0.05$. There was no significant difference in the mean serum CTX at 36 weeks and postpartum (2.35, 2.27 ng/ml) respectively (Table 1).

Table 1. — *A paired sample t-test comparing bone turnover markers and 25- OH vitamin D at 36 weeks and after delivery.*

Test	At 35-37 weeks	Postpartum	*p* value
25 OH vitamin D (mean)	35.72	28.06	0.114
Osteocalcin (mean)	14.1	16.49	0.05
CTX (mean)	2.28	2.27	0.975
PTH	3.528	4.26	0.372

25 OH vitamin D: 25 hydroxylase vitamin D. Bone turnover markers (BTM): psteocalcin (bone formation marker); CTX: (bone resorption marker). PTH: parathormone.

Discussion

BTMs had been validated [7] to reflect bone formation and resorption, and osteocalcin concentrations (a marker of bone formation) to be significantly correlated with bone mineral density of the spine [7].

The presumed worrisome radiation exposure risk halted extensive bone mineral density studies during pregnancy. Recently, To *et al.* and Kraemer *et al.* measured bone mass twice with quantitative ultrasonometry (QUS) of the heel (os calcaneus) during pregnancy and observed a reduction in bone mass from early to late third trimester [8, 9]. Although, a patient's current bone density is an important predictor of fracture risk [10, 11], however, it will not indicate the anticipated rate of bone loss.

Markers of bone turnover may be useful in predicting rates of bone loss [12-18], and if increased rapidly, the patient will have a higher fracture risk. Sex steroids play a key role in the bone remodeling process, Glover *et al.* [19] and de Papp *et al.* [20], in their studies, confirmed a drop in BTMs with the use of oral contraceptives and the former investigators also showed a relation with being close to time to ovulation**.** This study revealed that an acute drop in sex steroids did not lead to an increase in bone resorption markers, instead it led to AN increase in bone forming markers. Could this be because there is a multitude of several micro-environmental molecular changes during pregnancy that tip the balance differently, or could it be the duration which affects the estrogen deficiency? An unexpected regulatory effects of estrogen centered at the level of the adaptive immune response has been reported [21]. An increase in reactive oxygen species (ROS) has been implicated in the increased resorption associated with estrogen deficiency, [22]. It has also been associated with activation of NF-kB, and increased production IL-1, IL-6, IL-7, TNF, prostaglandin E2, M-CSF, and RANKL, although the extent is still unclear [21].

A major swing in prostaglandin level occurs during pregnancy and close to time of delivery. Prostaglandins have biphasic effects on bone resorption and formation, but the dominant effects in vivo are stimulatory [23]. Prostaglandin production can be increased by inflammatory cytokines. Regulation may occur as a result of both varying production of agonists and in changes in the receptors or binding proteins (receptor antagonists) for these factors [23]. PTH also stimulates gene expression and increases the production of IL-6, IGF-1, an IGF-binding protein, IGF-BP-5, and prostaglandins [24]. Could it be that this complicated micro-environment is controlling the net effect on the level of bone turnover markers that occurs during pregnancy and immediate postpartum period? A question that needs to be addressed in future studies.

Conclusions

The studied group of women had a high prevalence of vitamin D deficiency; this was not accompanied by a change in BTM, and this may suggest that a change in the level of steroids may play a role that modify the expected interaction between vitamin D and BTM. Larger studies are needed.

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