Ph.D. THESIS

BONE METABOLISM DURING PREGNANCY AND LACTATION

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INTRODUCTION

The actual bone mass is determined by the peak bone mass and the rate of bone loss. Lower bone mass is associated with increased fracture risk. The value of peak bone mass is influenced by genetic as well as environmental factors e.g., nutrition, physical exercise, certain physiologic conditions, diseases and drugs. The attainment of peak bone mass in women typically takes place in the early 30s. Pregnancy and lactation often occur during or before this period of life.

The alimentary calcium intake and the skeleton of the mother are the likely sources of calcium for the developing fetal bones. Calcium demand, which is also high in neonatal life, is usually met with breast milk calcium. There are a substantial number of publications on bone mineral density in pregnancy and lactation. Publications on this topic suggest loss of maternal minerals during lactation, while available clinical and epidemiological studies have not unequivocally verified a decrease in bone mass nor an increased incidence of osteoporotic fractures later in life.

AIMS OF THE STUDY

The purpose of this study was to monitor the changes in BMD, hormonal status and bone turnover markers during pregnancy, lactation and postweaning in a prospective manner at the Regional Osteoporosis Center of Debrecen, Hungary.

PATIENTS AND METHODS

A prospective study in 38 healthy Caucasian women was performed during their first full term pregnancy until 12 months postpartum. We recruited women intending to conceive within 3 months. All became pregnant, carried to term, gave birth to a child, and breast-fed for different durations. Exclusion criteria included: history of treatment for infertility, pregnancy induced hypertension, gestational diabetes, premature birth, twin pregnancy, complications during delivery, history of endocrine, hepatic, renal, respiratory, heart diseases and taking medication which might have affected bone metabolism.

The time during which the mother provided two thirds of the needed energy intake per kilogram of infant weight by breast-feeding was considered the lactation period. Participants were grouped according to the duration of lactation: a) none to less than 1 month, b) 1 to 6 months and c) more than 6 months. Participants were interviewed for past and current diseases, medication used, coffee consumption, smoking habits and a dietary questionnaire was also administered to determine the daily calcium intake. Morning blood and urine samples were obtained for laboratory tests and BMD measurements were carried out: i.) within 3 months prior to the conception (Baseline), ii.) between 22^{nd} and 24^{th} weeks of gestation (G), iii.) within 6 days of delivery, iv.) at 6 months (PP6) and v.) at 12 months postpartum (PP12).

BMD measurements were carried out using the LUNAR DPX-L dual-energy X-ray absorptiometry (DXA) densitometer (Madison, USA). Daily standardized measurement of the LUNAR phantom and HOLOGIC anatomical spine-phantoms served as quality control of the bone densitometer. The coefficient of variation (CV) of the technique at our institute was 0.8%, using a phantom measured thrice a week during the two year period of this prospective study. Measurements at both the lumbar spine (PA: L_2-L_4 [LS]) and the forearm (distal 33% [RD] and ultra-distal [RUD] region of the radius) were made at the baseline, delivery, PP6 and PP12 visits. At visit G, i.e., in mid pregnancy the DXA examination was carried out only at the forearm.

The BMD was expressed in g/cm^2. Follow up results were compared to baseline and previous measurements. The differences in BMD were calculated as a percentage of the baseline values.

Morning blood and urine samples were obtained for laboratory tests: i.) within 3 months prior to the conception (Baseline), ii.) between 22^{nd} and 24^{th} weeks of gestation (G), iii.) within 6 days of delivery, iv.) at 6 months (PP6) and v.) at 12 months postpartum (PP12).

Biochemical markers of bone turnover are reliable indices for measuring changes in bone formation and bone resorption. Due to limitations in the use of bone densitometry during pregnancy biochemical markers of bone turnover provide an excellent alternative to examine the state of the skeleton during this physiologic state. Blood samples were obtained for measurement of serum 25-hydroxyvitamin D (25-OH-D) using the ^{125}I RIA Kit, Incstar Corporation, USA (Intra-assay CV: <10%; Inter-assay CV: <12%); Parathyroid hormone (PTH) using CoTube PTH IRMA, Bio-Rad Diagnostic Group, USA (Intra-assay CV: <7%; Inter-assay CV: <13%); Bone

specific Alkaline Phosphatase (BSAP) using ALKPHASE-B, Metra Biosystems, Inc., USA (Intra-assay CV: <7%; Inter-assay CV: <9%); Osteocalcin (OC) using ^{125}I-OSTEOCALCIN RIA Kit, Institute of Isotopes, Hungary (Intra-assay CV: <2%; Inter-assay CV: <6%); Procollagen I carboxypeptides (PICP) using the ^{125}I RIA Kit, Orion, Finland (Intra-assay CV: <6%; Inter-assay CV: <8%), serum calcium, phosphate and creatinine were measured by standard methods. Urine was collected to measure Deoxypyridinoline crosslinks (D-Pyr) using Pyrilinks D, Metra Biosystems, Inc., USA (Intra-assay CV: <9%; Inter-assay CV: <5%) and calcium levels. The normal reference ranges were taken as mentioned in the different kits used.

Descriptive statistics (mean, standard deviation, 1st and 3rd quartiles, and range) were calculated for all continuous variables. During pregnancy the three lactation groups were considered as one and subsequently the statistical analysis was carried out. The BMD values were compared to each other within a given lactation group and between the different lactation groups. Analysis of variance for repeated measurements was performed for comparison along time. Correlation for two variables was analyzed by the linear correlation and regression analyses. Statistical significance was considered at $p < 0.05$. Statistical analyses were performed with PC-SAS for Windows (Statistical Analysis System) version 6.12.

RESULTS

The mean age (range) of the women participating in the study at baseline was 26 (19-36) years, BMI mean (± SD) was 24.4 (± 2.7) kg/m^2, age at menarche (mean, range) was 13 (10-15) years and weight gain (mean ± SD) during pregnancy was 12.5 (± 3.2) kg. The average daily calcium intake at baseline was comparable to the recommended calcium intake. The patient characteristics for each group are given in table I. There were no statistical differences between the groups except for duration of lactation and post partum amenorrhea ($p<0.001$).

The results were analyzed individually in each woman and by groups. The absolute BMD values, during pregnancy, at each site and visit are shown in table II. The absolute BMD values and the percentage change, during lactation, at each site, visit and group are shown in table III.

During pregnancy, there was significant difference between baseline and delivery ($p < 0.001$) in the BMD values measured at LS. There was a significant difference in the BMD values between gestation and delivery at RD ($p < 0.001$) and RUD ($p < 0.001$). Between baseline and delivery BMD decrease of 2.1%, 3.8% and 3.8% at LS, RD and RUD, respectively was observed.

In Group I, there was no statistically significant difference between the BMD values measured at LS and RD between the visits following pregnancy. At the RUD there was significant difference between BMD at delivery and PP12 visits ($p<0.05$). The RUD BMD increased by 5.0% between delivery and PP12.

In Group II, there was significant decrease of BMD at LS between delivery and PP6 visits ($p<0.001$) and significant increase between PP6 and PP12 ($p<0.05$). The change in the LS BMD from delivery to the end of the study was -2.6%. The BMD dropped (4.9%) till PP6 then increased by 2.3% as measured at PP12. At the RD there was no significant difference in the BMD values. The RUD BMD dropped (4.3%) till PP6, then increased by 3.1% as measured at PP12. At the RUD there was significant increase in BMD between PP6 and PP12 visits ($p<0.05$).

In Group III, at the LS there was significant decrease ($p<0.01$) in the BMD between delivery and PP6, PP6 and PP12. The BMD loss continued throughout the study period, the largest part of which took place between delivery and PP6 (7.4%). At the RD there was no significant difference in the BMD values. Whereas at RUD there were significant differences in the BMD between delivery and PP6 ($p<0.05$) and delivery and PP12 visits ($p<0.01$). The RUD BMD dropped (4.9%) till PP6 then increased by 3.0% as measured at PP12.

Further comparing the BMD between different groups measured at the same visit showed significant difference in the LS BMD values at PP6 visit between Group I and II, and Group I and III ($p<0.001$) and Group II and III ($p<0.05$). The same results were found at PP12 as well. At the RD there was no significant difference in BMD values. At the RUD there was a significant difference in the BMD values at PP6 between Group I and III ($p<0.01$)

Linear correlation and regression analyses showed that the duration of lactation correlated strongly with the duration of postpartum amenorrhoea ($r = 0.896$ $p<0.001$). Furthermore, the duration of postpartum amenorrhoea and the duration of lactation

correlated to the LS bone loss between delivery and PP12 ($r = -0.729$ and $r = -0.727$, $p<0.001$ respectively).

The biochemical variables were compared between different visits (table IV and V). There was no significant difference in the values of urinary calcium/creatinine and serum calcium, phosphate and 25-OH-D between the different visits during the study. PTH values significantly increased between baseline and PP12 ($p < 0.05$). So did the OC levels between baseline and delivery ($p < 0.01$), baseline and PP6 ($p < 0.01$), G and delivery ($p < 0.05$), G and PP6 ($p < 0.001$), and PP6 and PP12 ($p < 0.05$) visits. There were significant differences in the BSAP values between baseline and delivery ($p > 0.001$), baseline and PP6 ($p < 0.005$), G and delivery ($p < 0.001$), G and PP6 ($p < 0.01$), delivery and PP6 ($p < 0.005$) and delivery and PP12 ($p < 0.001$) visits. Also in the PICP values between baseline and delivery ($p < 0.01$), baseline and PP6 ($p < 0.01$), G and delivery ($p < 0.05$), G and PP6 ($p < 0.05$), delivery and PP12 ($p < 0.05$) and PP6 and PP12 ($p < 0.05$) visits. D-Pyr values differed between G and delivery ($p < 0.05$) and delivery and PP6 ($p < 0.05$) visits.

Table I. Patient characteristics

Patient Characteristics	**Lactation Duration (months)**		
	0-1 (n=7)	1-6 (n=11)	>6 (n=20)
Age, years (mean, range)	24.7 (20-31)	23.8 (19-29)	24.1 (20-36)
Baseline BMI, kg/m^2 (mean ± SD)	25.0 (± 3.2)	24.5 (± 1.8)	27.1 (± 2.9)
Daily calcium intake (baseline), mg (mean, range)	1350 (890-1760)	1250 (780-1680)	1290 (810-1530)
Age at menarche, years (mean, range)	12.6 (10-15)	13.1 (11-15)	13 (11-15)
Weight gain during pregnancy, kg (mean ± SD)	12.4 (± 5.4)	11.5 (± 3.9)	13 (± 3.2)
Weight of newborn, kg (mean ± SD)	3217 (± 360)	3202 (± 247)	3337 (± 380)
Time of the first postpartum menstrual bleeding, months (mean, range)	2.5 (1-3)	6.5 (1-8)	13 (7-18)
Duration of lactation, months (mean, range)	0.7 (0-1)	3.8 (2-5)	9.1 (7-12)

Table II. The BMD values at radius distal 33% (radius D), ultradistal radius (radius UD) and the lumbar spine (L2-L4) at baseline, during 22^{nd}-24^{th} week of gestation and within a week after delivery in all the patients studied (n = 38). The baseline value is used to express percent change.

Regions	**Measurement Period**					
	Baseline		Gestation		Delivery	
	BMD (g/cm^2)± SD	% ± SD	BMD (g/cm^2)± SD	% ± SD	BMD (g/cm^2)± SD	% ± SD
Radius D	0.682 ± 0.043	100	0.683 ± 0.044	100.1 ± 0.8	0.656 ± 0.041	96.1 ± 2.1
Radius UD	0.366 ± 0.040	100	0.364 ± 0.041	99.4 ± 1.35	0.352 ± 0.042	96.2 ± 1.6
L2-L4	1.126 ± 0.085	100	-	-	1.102 ± 0.089	97.9 ± 1.6

Table III. The BMD values at radius distal 33% (radius D), ultradistal radius (radius UD) and the lumbar spine (L2-L4) within a week after delivery, at 6 months postpartum and 12 months postpartum in the three lactation groups. The baseline value is used to express percent change.

Lactation duration (months) **Regions**	**Measurement Period**					
	Delivery		6 months postpartum		12 months postpartum	
	BMD (g/cm^2)± SD	% ± SD	BMD (g/cm^2)± SD	% ± SD	BMD (g/cm^2)± SD	% ± SD
0-1 (n = 7) (Group I)						
Radius D	0.646 ± 0.035	96.4 ± 1.9	0.605 ± 0.033	97.8 ± 2.1	0.663 ± 0.025	99.0 ± 1.4
Radius UD	0.337 ± 0.025	95.6 ± 1.5	0.353 ± 0.020	100.2 ± 1.1	0.354 ± 0.024	100.6 ± 0.4
L2-L4	1.114 ± 0.061	98.5 ± 1.0	1.120 ± 0.068	99.9 ± 1.1	1.135 ± 0.061	102.6 ± 1.0
2-6 (n = 11) (Group II)						
Radius D	0.672 ± 0.040	97.1 ± 2.4	0.675 ± 0.045	97.6 ± 1.5	0.688 ± 0.053	99.4 ± 2.6
Radius UD	0.373 ± 0.051	96.5 ± 2.0	0.357 ± 0.054	92.4 ± 3.2	0.368 ± 0.045	95.5 ± 3.4
L2-L4	1.131 ± 0.091	97.7 ± 1.4	1.076 ± 0.108	92.8 ± 3.3	1.101 ± 0.112	95.1 ± 3.7
>6 (n = 20) (Group III)						
Radius D	0.650 ± 0.042	95.5 ± 1.7	0.657 ± 0.040	96.6 ± 1.8	0.662 ± 0.043	97.3 ± 2.1
Radius UD	0.349 ± 0.038	96.2 ± 1.4	0.332 ± 0.035	91.7 ± 3.2	0.342 ± 0.038	94.5 ± 3.0
L2-L4	1.096 ± 0.078	97.9 ± 1.9	1.015 ± 0.100	90.5 ± 4.2	0.987 ± 0.088	88.0 ± 3.8

Table IV. Basic laboratory results of the mothers that lactated for more than 6 months (lactation group III) during the different follow-up periods.

Laboratory results (mean ± SD) (n = 20)	**Baseline**	**Gestation**	**Delivery**	**6 months postpartum**	**12 months postpartum**
Se Calcium, mmol/l	2.30 ± 0.08	2.30 ± 0.10	2.40 ± 0.12	2.42 ± 0.11	2.32 ± 0.10
Se Phosphate, mmol/l	1.20 ± 0.08	1.20 ± 0.07	1.21 ± 0.13	1.30 ± 0.11	1.32 ± 0.27
Ur Calcium/creatinine, mmol/mmol	0.23 ± 0.12	0.22 ± 0.11	0.24 ± 0.20	0.21 ± 0.15	0.29 ± 0.13

Table V. Hormone and Biochemical Markers of Bone Turnover results during the different follow-up periods.

Laboratory results (mean (1st Quartile – 3rd Quartile))	**Baseline**	**Gestation**	**Delivery**	**6 months postpartum**	**12 months postpartum**
Se 25-OH-D, ng/ml	29.0 (22-35)	27.4 (21-31.5)	31.9 (24-39)	29.9 (23-35)	26.8 (20.2-34.5)
Se PTH, pmol/l	2.2 (1.6-2.7)	3.0 (2.2-2.8)	2.8 (2.3-3.1)	3.0 (2-3.6)	3.4 (2.7-4)
Se Osteocalcin, ng/ml	9.1 (4.6-11.2)	9.8 (6-10.7)	17.9 (14.3-12.2)	22.3 (18.7-23.6)	14.82 (11.7-19.6)
Se BSAP, U/l	6.3 (6-6.6)	7.1 (4.8-8.4)	24.6 (15.8-26.2)	14.6 (11.3-19.2)	9.2 (8.5-9.4)
Se PICP, µg/l	227.3 (175.5-289.8)	692.4 (617.4-964.1)	1699.5 (1033.2-1778.7)	1733 (964.1-1986.9)	502.2 (326.3-675.6)
Ur D-Pyr, nmol/mmol creatinine	10.0 (7.2-12.4)	8.6 (6.5-10.8)	20.5 (12.3-24)	8.4 (5-11.4)	9.5 (8.2-10.4)

25-OH-D: 25 hydroxyvitamin D; PTH: Parathyroid hormone; OC: Osteocalcin; BSAP: Bone specific alkaline phosphatase; PICP: Procollagen I carboxypeptides; D-Pyr: Deoxypyridinoline crosslinks

DISCUSSION

Bone Mineral Density - Pregnancy

The three groups chosen made it possible to compare the BMD changes during pregnancy and lactation among women who breast fed for less than a month, between 1 and 6 months and between 6 and 12 months.

Concerns about fetal radiation exposure have resulted in few studies of changes in maternal bone mass during pregnancy; these studies used techniques that are far less precise or reproducible than the current standard, DEXA. Of the scant data available, an early study used x-ray spectrophotometry of the radius and femur to demonstrate a progressive decrease on trabecular bone density during pregnancy. Using more modern techniques, prospective studies of bone density during pregnancy did not find a significant change in cortical or trabecular bone density, as determined by single photon absorptiometry (SPA) and/or dual photon absorptiometry (DPA), respectively. Another study found a significant decrease in BMD of the femoral neck and radial shaft, but no changes in lumbar bone density, by comparing preconception SPA and DPA measurements to those taken 6 weeks postpartum. Most recently cross-sectional and longitudinal studies have found a progressive decrease during pregnancy in indices thought to correlate with BMD, as determined by ultrasonographic measurements of the os calcis in all three trimesters.

Naylor et al reported an increase in BMD at cortical sites and a decrease in BMD at trabecular bone sites during pregnancy. Lamke et al reported loss in trabecular but not cortical bone during pregnancy, measuring two sites at the radius. Others have reported decreased BMD at the radial shaft or no change in BMD of the radius. Lumbar spine BMD has been shown to decrease during pregnancy by 3.3%, a finding consistent with our findings of decreased BMD at the spine. In a prospective study, Sowers et al reported no significant change in proximal femur BMD with pregnancy. During pregnancy, we found a significant loss of BMD both at the trabecular and cortical sites.

It has been suggested that a sample size of greater than 25 would be necessary to detect the expected 3-4% difference in BMD during pregnancy, as such our study is in a position to address this subject. In a study of changes in trabecular bone architecture in women during pregnancy by Shahtaheri et al reported early temporary bone loss through trabecular thinning which was restored entirely through addition of new trabeculae to produce a modestly more complex system of thinner more numerous bars by term.

Bone Mineral Density - Lactation

In our study, among women breast feeding for less than a month the LS and RUD BMD loss was recovered by the 6th month postpartum, whereas recovery at the RD continued till 12 months postpartum at which point this loss was almost regained.

The group that breast fed for up to 6 months postpartum, showed continued bone loss until the 6th month postpartum at LS and RUD, after which both areas showed increase in bone mass but failed to attain the baseline value. Whereas at the RD bone loss was observed only till the first week postpartum after which it almost recovered to baseline level by 12 months postpartum.

Those who breast-fed till 12 months postpartum showed recovery in bone mass from delivery and 6 months postpartum at RD and RUD, respectively, but failed to reach the baseline BMD by 12 months postpartum, whereas the LS continued to lose BMD until 12 months postpartum.

In prospective studies a consistent bone loss was observed during extended breast-feeding. One of the studies reported a 15% mid radial bone loss (with SPA) between 2 and 16 weeks of lactation in a teenage group. Another 2 studies have noted a striking BMD loss during the first six months of full lactation with a subsequent recovery from this loss. In our study, loss of BMD was noted at 2 sites in women lactating for the first six months but failed to recover this loss at the LS and the RUD at 6 months postpartum but did almost regain the bone loss at the RD.

Most recent studies have further noted that although there is loss in bone mass during lactation of 6 months it is usually recovered by six months thereafter. Kolthoff et al observed 59 lactating women for 18 months postpartum and have reported that women lactating for > 6 months recover bone loss during extended periods after lactation.

The long-term implications of the obvious bone loss especially during prolonged lactation needs clarification, whether it is an increased risk to bone health later in life or it is only a challenge which typically offset by compensating mechanisms. A recent study suggests that BMD levels can be sustained in the presence of the rapidly changing hormone environment associated with multiple pregnancies accompanying lactation events without a recovery interval.

In our study different lactating groups were compared and a significant difference was found in the bone mass at the sites studied between the lactating groups at similar times of measurement, as such non-lactating postpartum women are compared to their lactating

counterparts. We suggest that calcium needed for fetal skeletal growth during pregnancy was gained from maternal trabecular and cortical sites and that needed for infant growth during lactation was drawn mainly from the maternal trabecular skeleton in our patients.

Biochemical markers of bone turnover

Studies of bone turnover markers suggest substantial biological activity of bone during pregnancy. It has been shown that OC levels were comparably similar to controls in the first trimester, declined in the second trimester, and then recovered in the third trimester to levels observed in the normal non-pregnant controls. We found that from baseline till delivery the OC levels almost doubled and in the 22-24th gestational week the levels were higher than baseline.

In publications, BSAP was found low in the first trimester and either remained low or rose to normal or above in the last trimester. We observed that BSAP showed gradual increase till the 22-24th gestational week and then rapidly increased until delivery.

Published urinary D-pyr levels are low in the 1st trimester but rise steadily to peak values up to twice the normal in the last trimester. In our patients there was a significant increase between 22-24th week and delivery.

PTH levels have been found by others to be low-normal in the serum of pregnant women in all 3 trimesters. We found no significant elevation of PTH during pregnancy.

In a comprehensive paper serum 25-OH-D levels were significantly higher in the 3rd trimester compared with prepregnancy. We found that there was no significant difference in the values of 25-OH-D between the different visits during the study.

As such we found increased bone turnover during pregnancy as reported recently by Naylor et al. The 3rd trimester increase in bone turnover corresponds to time of peak rate of calcium transfer to the fetus and may result from mobilization of skeletal calcium stores to supply the fetus.

During extended lactation, Sowers et al showed that OC and BSAP reached zenith at 4-6 months of lactation and subsequently fell to baseline by 18 months postpartum. We found that OC peaked at 6 months of lactation (+144.6%) and decreased to 62.5% as measured at 12 months of lactation. Whereas, BSAP reached zenith at delivery and subsequently tapered off to about 146% of the baseline value at 12 months of lactation. A measurement at 18 months would have been useful to elucidate the pending features.

PTH has been found to be reduced 50% or more in lactating women in both cross-sectional and longitudinal studies. In our patients there was a significant increase in PTH levels at 12 months postpartum in lactating women as compared to values at baseline, although the mean values remained in the PTH reference range.

In literature PICP decreased in 1st and 2nd trimester; and increased in last trimester. We found that there was a rapid increase (almost by 650%) up to delivery that started to decrease only after 6 months postpartum.

In the published studies D-Pyr is elevated 2-3 fold during lactation and is higher than the levels attained in the 3rd trimester. In our patients there was a significant increase between delivery and the 6th month of lactation.

In summary, our findings show that the bone formation markers are elevated through out pregnancy and OC and PICP are elevated until 6 months postpartum. Whereas the resorption marker decreases towards mid-gestation and rises again towards delivery to fall again below the baseline values during lactation. The difference in our findings as compared to the others may in part be attributed to the small number of women that we studied and the sample number for a few comparisons may well have fallen below the limit of safe statistical handling limit.

The long-term implications of the obvious bone loss especially during prolonged lactation needs clarification, whether it is an increased risk to bone health later in life or it is only a challenge which is typically offset by compensating mechanisms. Sowers et al reported that by 18 months postpartum there was no difference in values of bone turnover markers among women who lactated for at least 6 months and those that did not. Moreover, sequential full term pregnancies also need to be evaluated in the light of calcium and bone homeostasis.

The high maternal bone turnover may suggest that the calcium needed for infant growth during pregnancy and lactation may be drawn at least in part from the maternal skeleton.

Based on speculation, in the time of building peak maternal bone mass, the effect of pregnancy and lactation may be spontaneously and completely compensated. The mechanisms that are involved in the promotion of bone health in this period of life need to be further studied.

PUBLICATIONS

List of articles used in the thesis:

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