Osteoporosis Int (1993) Suppl. 1: S44–47

Osteoporosis
International

Effect of Pregnancy and Lactation on Maternal Bone Mass and Calcium Metabolism

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Introduction

During pregnancy and lactation there is increased demand from the fetus and neonate for calcium (Ca) and inorganic phosphate (Pi) from maternal sources. During the last trimester of pregnancy and during established lactation 5–8 mmol Ca and 3–5 mmol Pi are transferred each day to the fetus or infant. To meet the demands for Ca and Pi during pregnancy and lactation the maternal homeostatic system can respond to make Ca and Pi available from only three sources: (1) increased dietary intake with or without increased efficiency of absorption; (2) decreased urinary excretion as a result of increased tubular resorption of Ca and Pi; and (3) increasing bone turnover with a net loss of bone. There is surprisingly little information on the relative importance of each of these sources of Ca and Pi in human pregnancy and lactation [1].

The effects of parity and lactation on maternal bone mass are variable [reviewed by 2]. Confounding factors such as the skeletal site for measurement of maternal bone mineral content, age, dietary Ca intake and level of physical activity have contributed to this variability. Occasionally this bone loss during pregnancy and lactation can be so severe that skeletal complications including skeletal fractures can develop [3,4]. Our own study on Ca metabolism and of the arm bone mineral density (FBMD) in 40 women at 6 months of lactation and after weaning compared with 40 age-matched controls found that in lactation there is a selective reduction (of 7%) in FBMD at an ultradistal site containing approximately 60% cancellous bone, but not at two or more proximal, chiefly cortical, bone sites on the forearm [5]. This bone loss was associated with increased bone turnover affecting both bone resorption (increased fasting hydroxyproline excretion [Hyp_E]) and bone formation (increased serum osteocalcin [OC] and increased plasma alkaline phosphatase [AlP]) and renal conservation of both Ca (decreased fasting Ca excretion [Ca_E]) and Pi (increased renal Pi threshold concentration [Tm_{Pi}/GFR]) with a resultant increase in plasma Pi but not in plasma Ca. There were no differences between the groups in serum parathyroid hormone (PTH; intact and mid-molecule) or in the vitamin D metabolites, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D (1,25-D). Following weaning there was an early (2 months) normalization of bone resorption and renal Pi handling with continuing elevated bone formation and renal Ca conservation, associated with a rise in intact PTH. There was later (4–6 month) recovery in ultradistal FBMD associated with normalization of bone formation, but renal Ca conservation and elevated intact PTH levels persisted.

The aims of our subsequent longitudinal study beginning at the end of the first trimester of pregnancy through to 6 months after weaning were (1) to measure serially the maternal intake and efficiency of Ca absorption, urinary Ca excretion and FBMD; (2) to investigate the hormonal mechanisms responsible for the changes in maternal Ca, Pi and bone metabolism; and (3) compare and contrast these maternal responses in pregnancy and lactation.

Study Design, Methods and Results

Three groups of women were studied: 37 women during pregnancy and lactation and after weaning using the study protocol shown in Table 1; 19 women who elected to bottlefeed their infant and had FBMD studies done at 2 and 24 weeks post-partum; and 27 control women on whom FBMD, fasting blood and urine collections, 24-h urine collections and measurements of fractional absorption of Ca (FA-Ca) were done. A repeat FBMD study was done 1 year after the initial study in the control women.

Table 1. Design of the longitudinal study

Study	Pregnancy		Lactation		Weaning
	14 weeks	36 weeks	6 weeks	24 weeks	8/24 weeks
FBMD	*	*	*	*	*
Fasting blood/urine	*	*	*	*	*
24-h urine	*	*	*		
FA-Ca	*	*			
4-day diet record	*	*	*		
Milk production	*				

FBMD, forearm bone mineral areal density; FA-Ca, fractional absorption of calcium.
An asterisk indicates that the study was done at the time shown.

Four-day weighed diet records were collected and nutrient intake was calculated form these coded diet records using the NUTTAB data base from the Commonwealth of Australia Department of Health. FA-Ca was measured at 36 weeks of pregnancy and 24 weeks of lactation using a dual stable Ca isotope technique developed by us [6,7]. FBMD,expressed in units of 'mg mineral/cm^2 scanned bone area' was measured on the nondominant forearm of each subject by ^{125}I single-photon absorptiometry using a Mølsgaard Model BMA 1100 Bone Mineral Analyser with scanning and analysis software developed by the authors [8]. Three radio-ulnar regions of the distal forearm are measured: an ultradistal site comprised of approximately 60% cancellous bone, a distal site immediately proximal to the 8-mm point of the ultradistal site (<5% cancellous). Fasting 2-h urine collections with mid-point blood samples were done using the method of Nordin [9] as previously described [5]. Daily milk production was determined by the maternal weighing method with correction for evaporative water loss [10]. Six milk samples were collected from each woman during this 24-h period and the Ca and Pi content determined in weighed, ashed milk samples.

In pregnancy the dietary Ca intake was near the Australian National Health and Medical Research Council recommended dietary intake (RDI) of 27.5 mmol/day and above the mean control intake of 21.2 mmol/day. Dietary Ca intake was unchanged when measured in lactation compared with pregnancy. FA-Ca was increased in late pregnancy (72.5% ± 1.7%, mean ± SEM) compared with both control (58.7% ± 2.3%) and lactating (63.5% ± 1.8%) women [7]. Surprisingly, FA-Ca was not increased in lactation compared with control women.

Urinary Ca excretion was increased in late pregnancy and decreased in lactation compared with control women. Fasting Ca_E was normal during pregnancy but reduced in lactation. Daily Pi excretion was increased in both pregnancy and lactation compared with controls. The fasting Tm_{Pi}/GFR was markedly increased in lactation compared with both pregnancy and control women. Daily urinary sodium excretion was the same in control, pregnant and lactating women. The mean 24-h milk Ca secretion was 5.1 mmol/day.

Fasting plasma Ca was decreased in late pregnancy but normal during lactation. Plasma Pi, on the other hand, was normal during pregnancy but increased during lactation, following the changes in Tm_{Pi}/GFR. The serum levels of intact PTH and 25-hydroxyvitamin D were the same as in controls throughout the pregnancy and lactation. Serum 1,25-dihydroxyvitamin D (1-25-D) and vitamin D binding protein were markedly elevated in late pregnancy but normal in lactation. The measured level of free 1,25-D and the calculated free 1,25-D index were also evaluated in pregnancy.

There was no change in FBMD at any of the three sites during pregnancy. During lactation, however, there was an overall mean loss of 3% in FBMD at the ultradistal site (containing ~60% cancellous bone) with no change in the more proximal, chiefly cortical bone sites (in accordance with our earlier study [5]). This loss occurred during the period from 36 weeks of pregnancy to 24 weeks of lactation. In contrast FBMD at the ultradistal site increased slightly in the bottlefeeding women from 2 to 24 weeks post-partum. There was no change at either of the other two more proximal sites. There was no change in FBMD at any of the three sites in the 17 control women restudied after 1 year.

Increased bone turnover affecting both bone resorption (increased fasting Hyp_E) and bone formation (increased serum OC and increased plasma AlP) were seen at both 6 and 24 weeks of lactation. The increases in Hyp_E and AlP seen at 36 weeks of pregnancy are due to increased turnover of soft tissue collagen (i.e. uterus and skin) and to the placental isoenzyme of AlP, respectively.

Discussion

In this study we could find no evidence of any loss of maternal bone or increase in bone turnover during *pregnancy*. There was an increase in dietary Ca intake and FA-Ca, the latter effect probably mediated by the increased 1,25-D level. The only significant change in Ca biochemistry was an increased daily urinary excretion of Ca (i.e. physiological hypercalciuria). This probably results from

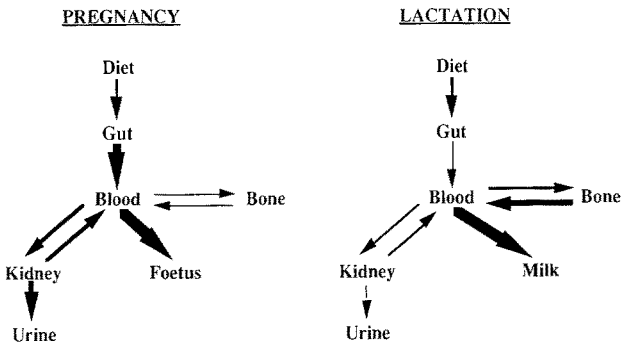

Fig. 1. The role of gut absorption of Ca, kidney excretion of Ca and bone turnover in providing Ca for the fetus during pregnancy or for milk during lactation. The size of the *arrow* indicates the relative magnitude of the flux of Ca.

the increase in GFR together with a slight rise in filtered load after oral Ca [11]. It appears that the increased intakes of Ca and Pi during pregnancy coupled with increased FA-Ca are sufficient to meet the demands for transfer of Ca and Pi across the placenta (Fig. 1).

In *lactation*, however, bone turnover increases and cancellous bone loss occurs. This observation in our current longitudinal study confirms the cancellous bone loss seen in the forearm in our previous cross-sectional study in lactation [5]. Hayslip et al. [12] reported, in a study on 12 breastfeeding women, a 6.5% reduction in the bone mineral content (BMD) of the lumbar spine at 6 months of lactation compared with 2 days post-partum. There was no change in lumbar spine BMC, over the same period, in 7 bottle-feeding women or in the BMC at two cortical bone sites in the radius in either group of women. This study did not report any data on the recovery, if any, of lumbar spine BMC after weaning. As in our study there was no loss of forearm cortical bone density and the loss at the ultradistal site is not seen in women who do not breastfeed after the birth of their baby. The rate and extent of the recovery of the bone lost during lactation is still not clear. In this current study we found that FBMD at the ultradistal site had not returned to the initial value by 6 months after weaning in the 19 women. If this bone loss is not recovered after weaning this would result in a net deficit for each cycle of pregnancy/lactation – a conclusion supported by a recent study that found a significant association between the total number of months of breastfeeding and low BMC in the lumbar spine [2]. If bone loss is recovered, after 6 months, this suggests the need to space future pregnancies to allow recovery to occur after weaning.

It is not clear what hormones are responsible for conservation of Ca and Pi during lactation. The fasting renal conservation of Ca is also maintained after an oral Ca load when there is suppression of both serum levels of intact PTH and bone resorption [11]. Serum intact PTH remained unchanged throughout the study. The effect of PTH and 1,25-D on bone may be enhanced during lactation by the withdrawal of estrogen in the early post-partum period. The low levels of estrogen do not afford any protection to bone from the resorptive actions of either PTH or 1,25-D. Serum growth hormone and thyroid hormone were not increased. There may be a role for parathyroid-hormone-related protein (PTH-RP) during lactation since it is expressed in the mammary gland [13] and found in high concentrations in milk [14]. PTH-RP may mediate the renal conservation of Ca and the increase in bone turnover but has a phosphaturic action on the kidney rather than reducing renal Pi excretion as we found. This issue will be resolved with the advent of reliable, sensitive and carefully characterized assays for blood PTH-RP in lactating women.

The most surprising finding was the normal FA-Ca during lactation. The demand for Ca and Pi is the same as in late pregnancy but FA-Ca and serum 1,25-D bioavailability are normal. Thus it appears that the Ca required for milk production is derived from dietary, renal and bone sources without enhanced absorption (Fig. 1).

Current studies are under way to address the following questions: (1) Is bone loss greater or less at weight-bearing sites and sites containing mainly cancellous bone in the skeleton? (2) Since an oral Ca supplement reduces bone resorption acutely will an oral Ca supplement prevent lactational bone loss? (3) Is lactational bone loss reversible after weaning? How long after weaning should a subsequent pregnancy be delayed to permit recovery of bone mass? (4) What is the hormonal basis of the lactational changes in Ca, Pi and bone biochemistry?

Acknowledgements. This project was supported by grants from the National Health and Medical Research Council, Sir Charles Gairdner Hospital Research Foundation.

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