Hormones and Healthy Bones
Joint Project of
National Osteoporosis Foundation and Association of Reproductive Health Professionals

Literature Review (January 2009)
Lactation and Bone Loss

1. Aynaci O, Kerimoglu S, Ozturk C, Saracoglu M. Bilateral non-traumatic acetabular and femoral neck fractures due to pregnancy-associated osteoporosis. *Arch Orthop Trauma Surg.* 2008;128:313-6.
   Abstract: Pregnancy-associated osteoporosis is a rare disorder and its pathophysiology remains unknown. We report a case of pregnancy-associated osteoporosis in a 27-year-old primiparous patient who revealed bilateral hip pain during early postnatal period. The plain radiographs and computerized tomography showed bilateral femoral neck and acetabular fractures. The diagnosis of osteoporosis was established by bone mineral density. Diagnostic work-up excluded a secondary osteoporosis. The case was treated successfully by bilateral cementless total hip arthroplasty. Bone mineral density increased after 2 years of treatment with calcium-vitamin D, calcitriol and alendronate. Diagnosis of pregnancy-associated osteoporosis should be suspected when hip pain occurs during pregnancy or in the post-partum period as it can lead to acetabular and femoral neck fractures.

2. Carranza-Lira S, Mera JP. Influence of number of pregnancies and total breast-feeding time on bone mineral density. *Int J Fertil Womens Med.* 2002;47:169-71.
   Abstract: OBJECTIVE: To analyze how the number of pregnancies and total breast-feeding time influence bone mineral density. METHODS: 50 healthy women aged 35 to 40 years were studied. Weight, height, number of term pregnancies, time since last pregnancy and breast-feeding time were analyzed. They were divided in three groups as follows: I: nulligravidas; II: with term pregnancies, but no breast-feeding; III: with term pregnancies, with breast-feeding. Bone absorptiometry was done on all, at lumbar column and femur. The WHO criteria were used to define osteopenia and osteoporosis. Comparison among the groups was done with Student's t-test for independent samples, and simple regression analysis was done for number of gestations, total breast-feeding time, time since last birth, and T-score at lumbar column and femur. RESULTS: The women were divided as follows: 15 in group I, 15 in group II, and 20 in group III. The average age was 37.7 +/- 1.5 years. No differences were found among the three groups in analyzed variables, when comparing bone mineral density, T- and Z-scores in L1-L4 average, femoral neck, trochanter, and Ward's triangle. There was no correlation among the number of gestations, total breast-feeding time, time since last birth, or T-scores at lumbar column and femur. CONCLUSION: The number of pregnancies and breast-feeding time do not affect bone mineral density.

3. Clemetson IA, Popp A, Lippuner K, Ballmer F, Anderson SE. Postpartum osteoporosis associated with proximal tibial stress fracture. *Skeletal Radiol.* 2004;33:96-8.
   Abstract: A 33-year-old woman presented with acute nonspecific knee pain, 6 months postpartum. MR imaging, computed tomography and radiography were performed and a proximal tibia plateau insufficiency fracture was detected. Bone densitometry demonstrated mild postpartum osteoporosis. To our knowledge these findings have not been described in this location and in this clinical setting. The etiology of the atraumatic fracture of the tibia is presumed to be due to a low bone mineral density. The bone loss was probably due to

pregnancy, lactation and postpartum hormonal changes. There were no other inciting causes and the patient was normocalcemic. We discuss the presence of a postpartum stress fracture in a hitherto undescribed site in a patient who had lactated following an uncomplicated pregnancy and had no other identifiable cause for a stress fracture.

4. Di Gregorio S, Danilowicz K, Rubin Z, Mautalen C. Osteoporosis with vertebral fractures associated with pregnancy and lactation. *Nutrition.* 2000;16:1052-5.
Abstract: Three cases of young women who developed severe vertebral osteoporosis after pregnancy and during lactation are described. These patients shared several features: a low-calcium diet during most of their lives, very-low body weight in two patients, and a positive family history of osteoporosis in two patients. Initial studies disclosed vertebral fractures, severely diminished bone mineral density of the spine (Z score = -3.3 to -4.1), and a less severely affected bone mineral density of the hip (Z score = -1.6 to -2.3). During the prolonged follow-up of these patients, treated with oral biphosphonates, vitamin D, and calcium, an improved clinical response with a marked recovery of spine bone mineral density was observed. Poor general nutrition, low calcium intake, and a positive family history of osteoporosis appear to be strong risk factors for pregnancy- and lactation-associated osteoporosis. Although the mechanism of action is uncertain, calcium, vitamin D, and antiresorptive agents may have been beneficial in the treatment of this severe disorder.

5. Dursun N, Akin S, Dursun E, Sade I, Korkusuz F. Influence of duration of total breast-feeding on bone mineral density in a Turkish population: does the priority of risk factors differ from society to society? *Osteoporos Int.* 2006;17:651-5.
Abstract: INTRODUCTION: Despite numerous studies on risk factors for osteoporosis the effect of breast-feeding on bone mineral density (BMD) is unclear. In this study our aim was to determine the influence of total duration of breast-feeding on BMD, and subsequent risk of osteoporosis. METHODS: A total of 1,486 postmenopausal women over the age of 40 were included in the study. Women with diseases or who were under drug treatments known to affect bone metabolism were excluded. The BMD of the lumbar spine and femoral neck were measured by dual-energy X-ray absorptiometry technique, using either the Norland XA-26 or Lunar DPX-IQ densitometers and were transferred to standard values. Patients were placed in groups of five with respect to the duration of their breast-feeding as never, 1-12 months, 12-24 months, 24-60 months, >60 months. RESULTS: One-way ANOVA test showed a significant difference between the lumbar spine and femoral neck BMD of these groups of women ($p<0.001$, $p<0.001$). Post hoc Bonferroni correction revealed that both the lumbar spine and femoral neck BMD results of women with longer duration of total breast-feeding were significantly lower than those of women with less duration of total breast-feeding. In subsequent analysis other potential risk factors were also considered in a multiple linear stepwise regression model. Years since menopause ($p<0.001$), weight ($p<0.001$), total duration of breast-feeding ($p<0.001$), and body mass index ($p=0.001$) were found to be the most important predictors for lumbar spine BMD; and age ($p<0.001$), weight ($p<0.001$), years since menopause ($p<0.001$), and total duration of breast-feeding ($p<0.001$) for femoral neck BMD. CONCLUSIONS: This study showed significant associations between total duration of breast-feeding and BMD. In conclusion, total duration of breast-feeding might be an important risk factor besides age, weight, and years since menopause in postmenopausal osteoporosis.

6. Ensom MH, Liu PY, Stephenson MD. Effect of pregnancy on bone mineral density in healthy women. *Obstet Gynecol Surv.* 2002;57:99-111.
Abstract: Despite numerous studies and case reports of changes in bone mineral density (BMD) during pregnancy, the postpartum, and lactation, controversy exists regarding the time course of BMD changes and recovery to baseline levels. The degree to which pregnancy affects BMD long-term remains unclear. Several influencing factors, including breast-feeding, length of amenorrhea after pregnancy, and parity, have been studied with respect to changes in BMD in healthy women. We conducted the first systematic review of its kind on this topic and evaluated the 23 identified citations according to the U.S. Preventive Services Task Force rating scale. Six studies qualified as Level II-2, 12 were Level II-3, and 5 were Level III. There seems to be good evidence that calcium is mobilized from the maternal skeleton to that of the developing fetus during pregnancy. However, the eventual return of BMD to prepregnancy values suggests that maternal bone loss may not be permanent. Results from the studies that specifically evaluated the effect of lactation on BMD were varied, ranging from a decrease in BMD to no change. Of the studies that evaluated the effect of parity on BMD, none found an association linking a greater number of pregnancies to greater decreases in BMD. Pregnancy-associated osteoporosis seems to be uncommon, based on the limited published reports. Overall, no long-term adverse clinical effects have been noted in healthy women who had at least one ongoing pregnancy, despite the good evidence that some bone loss does occur soon after delivery. Additional longitudinal studies need to be undertaken to provide more definitive information on the effects of pregnancy on BMD and risk of osteoporosis later in life.

7. Ghannam NN, Hammami MM, Bakheet SM, Khan BA. Bone mineral density of the spine and femur in healthy Saudi females: relation to vitamin D status, pregnancy, and lactation. *Calcif Tissue Int.* 1999;65:23-8.
Abstract: Bone mineral density (BMD) measurements of the anterio-posterior lumbar spine and the proximal femur using dual-energy x-ray absorptiometry, as well as relevant clinical and biochemical parameters, were determined in 321 healthy Saudi females in order to establish reference values and to study the effects of physical and lifestyle factors on BMD. Mean +/- SD of age, body mass index (BMI), number of pregnancies, and total duration of lactation were 35.4 +/- 11.3 years, 26.5 +/- 5.2 kg/m2, 3.1 +/- 3.1, and 23.7 +/- 42.4 months, respectively. Mean +/- SD of serum calcium, 25-hydroxyvitamin D (25OHD), and PTH levels were 2.37 +/- 0.09 mmol/liter, 24.5 +/- 17.2 nmol/liter, and 52.0 +/- 30.8 pg/ml, respectively. Peak BMD values were observed around age 35 years at the spine and earlier at the femur. Compared with USA females, Saudi females had lower weight-matched Z scores at the spine (-0.126 +/- 1. 078, P = 0.04), femoral neck (-0.234 +/- 0.846, P < 0.0001), and Ward's triangle (-0.269 +/- 1.015, P < 0.0001). Further, the prevalence of osteopenia and osteoporosis in subjects >/=31 years old were 18-41% and 0-7%, respectively, depending on the site examined. Severe hypovitaminosis D (25OHD level </=20 nmol/liter) was present in 52% of the subjects. However, there was no correlation between 25OHD level and BMD at any site. Parathyroid hormone (PTH) levels correlated significantly with 25OHD levels (r = -0.28, P < 0.0001) and with weight-matched BMD Z scores at the spine (r = -0.17, P = 0.005), femoral neck (r = -0.16, P = 0.007), and Ward's triangle (r = -0.2, P = 0.0008), suggesting that the distribution of 25OHD levels in the cohort is below the threshold needed for maintaining normal BMD. On the other hand, number of pregnancies and total duration of lactation correlated with weight-matched BMD Z scores at the spine (r = -0.17, P = 0.003; r = -0.1, P = 0.08, respectively). We conclude that BMD in healthy Saudi females is significantly lower than in their USA counterparts.

This may be due in part to increased number of pregnancies and longer duration of lactation together with prevalent vitamin D deficiency. http://link.springer-ny.com/link/service/journals/00223/bibs /65n1p23. html

8. Grimes JP, Wimalawansa SJ. Breastfeeding and postmenopausal osteoporosis. *Curr Womens Health Rep.* 2003;3:193-8.
Abstract: Bone loss associated with osteoporosis occurs with high frequency among the elderly and often results in debilitating fractures. A combination of lifestyle behaviors, genetic predisposition, and disease processes contributes to bone metabolism. Therefore, any discussion regarding bone health must address these factors. The impact of menopause on bone turnover has been generally well studied and characterized. Breastfeeding places significant stress on calcium metabolism and, as a consequence, directly influences bone metabolism. The most significant factors affecting bone mineral density (BMD) and bone metabolism are the duration and frequency of lactation, the return of menses, and pre-pregnancy weight. Although transient, lactation is associated with bone loss. As clinical guidelines and public health policies are being formulated, there is a compelling need for further investigation into the relationship of lactation, BMD, and subsequent risk of osteoporosis. Better understanding of this relationship will provide new opportunities for early intervention and ultimately help in the prevention of bone loss in postmenopausal women.

9. Hadji P, Ziller V, Kalder M, et al. Influence of pregnancy and breast-feeding on quantitative ultrasonometry of bone in postmenopausal women. *Climacteric.* 2002;5:277-85.
Abstract: OBJECTIVE: Reproductive factors such as parity and breast-feeding may be associated with low bone mass and osteoporotic fractures in later years. In this study, os calcis quantitative ultrasonometry was used to elucidate the relationship between parity, lactation and bone mass in postmenopausal women. DESIGN: This was a comparison study using subsequent matched pairs analysis as well as multiple linear regression analysis. The study was carried out at five centers in Germany. The study included 2,080 postmenopausal women (age (mean +/- SD) 58.8 +/- 8.2 years), who were attending for routine check-up and in whom diseases and drug treatments known to affect bone metabolism had been excluded. Methods and outcome measures: Women underwent quantitative ultrasonometry (QUS) measurement at the heel. Values of the ultrasonometry variables -speed of sound, broadband ultrasound attenuation and stiffness index -were calculated and compared for nulliparous and parous women and for women who had and had not breast-fed. Because of some significant intergroup differences, and to determine any effect of the number of live births and the duration of breast-feeding on ultrasonometry results, second analyses were undertaken using equally sized samples, matched for possible confounding variables such as age and body mass index (matched pairs). In these analyses, nulliparous women were compared with parous women, grouped according to number of live births, and women who had never breast-fed were compared with women who had breast-fed, grouped according to duration of breast-feeding. Furthermore, a multiple linear regression analysis was performed to examine the combined effects of reproductive factors on QUS variables. RESULTS: No statistically significant associations were found between ultrasonometry variables and parity or breast-feeding, even after controlling for confounding variables in matched-pairs analysis or in a multiple linear regression analysis.

10. Hellmeyer L, Ossendorf A, Ziller V, Tekesin I, Schmidt S, Hadji P. Quantitative ultrasonometry of the phalanges during pregnancy: a longitudinal study. *Climacteric.* 2006;9:446-51.
Abstract: OBJECTIVE: The aim of this study was to determine prospectively the change in results of bone ultrasonometry measurement during pregnancy in healthy German women.Study design Quantitative ultrasonometry (QUS) of the phalanges was performed in 60 healthy, pregnant women. Measurements of amplitude-dependent bone propagation velocity (speed of sound; AdSOS) and the bone transmission time (BTT) were performed during the three trimesters of pregnancy in 60 patients. RESULTS: During pregnancy, a significant increase in body weight and body mass index ($p < or = 0.001$) were observed. In accordance with bone ultrasonometry, a significant reduction in AdSOS was found in each trimester; AdSOS was significantly lower in the second and third trimesters compared with the first ($p < or = 0.001$). The BTT values also decreased significantly in the second and third trimesters compared with the first ($p < or = 0.001$). No significant influence was found of possible risk factors such as family risk of osteoporosis, previous pregnancies, age at menarche and prior use of oral contraceptives on QUS measurement results. CONCLUSIONS: During normal pregnancy, we found a significant reduction of quantitative ultrasonometry variables AdSOS and BTT in healthy pregnant women. This decrease had a large influence on the t score and Z score of QUS in our study and demonstrates therefore a possible clinical relevance. The decrease was independent of osteoporosis-related risk factors and the increase in body weight. More large-scale, prospective studies are needed to increase our knowledge about the mechanism of bone turnover during pregnancy and lactation.

11. Henderson PH 3rd, Sowers M, Kutzko KE, Jannausch ML. Bone mineral density in grand multiparous women with extended lactation. *Am J Obstet Gynecol.* 2000;182:1371-7.
Abstract: OBJECTIVE: We sought to assess whether the accumulation of multiple, frequent pregnancies and the accompanying repeated extended lactation events was a risk factor for low bone mineral density and osteoporosis. STUDY DESIGN: The study population consisted of 30 grand multiparous women who had borne at least 6 children and lactated for at least 6 months with each child, as well as 6 nulliparous, premenopausal women from a population of Finnish American women associated with the Laestadian Church in Washington State. The Church membership has not embraced contraception or extensive bottle-feeding, resulting in a group of women who are either pregnant or lactating during most of their adult reproductive lives. The medical history included the delivery date, birth outcome, infant birth weight, and number of months lactated for each pregnancy, as well as other health information. Bone mineral density of the lumbar spine, femoral neck, and radius was measured with the Hologic QDR 4500-C dual-energy x-ray absorptiometry scanner. Proc Genmod, SAS version 6.14 (Statistical Analysis Systems, Inc, Cary, NC), was used to perform a Wilcoxon test for a nonparametric analysis of covariance and significance adjusted for age and body size. RESULTS: The 2 study groups did not differ in terms of body mass index, history of smoking, or family history of osteoporosis and fracture, although the parous group was, on average, 8 years older than the nulliparous group ($P <.05$). The accumulation of repeated pregnancy and lactation events without a recovery interval was not associated with lowered bone mineral density or the presence of osteoporosis or osteopenia. CONCLUSIONS: This study suggests that bone mineral density levels can be sustained in the presence of the rapidly changing hormone environment associated with multiple pregnancies accompanying lactation events without a "recovery" interval.

12. Ip S, Chung M, Raman G, et al. Breastfeeding and maternal and infant health outcomes in developed countries. *Evid Rep Technol Assess (Full Rep).* 2007:1-186.
Abstract: OBJECTIVES: We reviewed the evidence on the effects of breastfeeding on short- and long-term infant and maternal health outcomes in developed countries. DATA SOURCES: We searched MEDLINE(R), CINAHL, and the Cochrane Library in November of 2005. Supplemental searches on selected outcomes were searched through May of 2006. We also identified additional studies in bibliographies of selected reviews and by suggestions from technical experts. REVIEW METHODS: We included systematic reviews/meta-analyses, randomized and non-randomized comparative trials, prospective cohort, and case-control studies on the effects of breastfeeding and relevant outcomes published in the English language. Included studies must have a comparative arm of formula feeding or different durations of breastfeeding. Only studies conducted in developed countries were included in the updates of previous systematic reviews. The studies were graded for methodological quality. RESULTS: We screened over 9,000 abstracts. Forty-three primary studies on infant health outcomes, 43 primary studies on maternal health outcomes, and 29 systematic reviews or meta-analyses that covered approximately 400 individual studies were included in this review. We found that a history of breastfeeding was associated with a reduction in the risk of acute otitis media, non-specific gastroenteritis, severe lower respiratory tract infections, atopic dermatitis, asthma (young children), obesity, type 1 and 2 diabetes, childhood leukemia, sudden infant death syndrome (SIDS), and necrotizing enterocolitis. There was no relationship between breastfeeding in term infants and cognitive performance. The relationship between breastfeeding and cardiovascular diseases was unclear. Similarly, it was also unclear concerning the relationship between breastfeeding and infant mortality in developed countries. For maternal outcomes, a history of lactation was associated with a reduced risk of type 2 diabetes, breast, and ovarian cancer. Early cessation of breastfeeding or not breastfeeding was associated with an increased risk of maternal postpartum depression. There was no relationship between a history of lactation and the risk of osteoporosis. The effect of breastfeeding in mothers on return-to-pre-pregnancy weight was negligible, and the effect of breastfeeding on postpartum weight loss was unclear. CONCLUSIONS: A history of breastfeeding is associated with a reduced risk of many diseases in infants and mothers from developed countries. Because almost all the data in this review were gathered from observational studies, one should not infer causality based on these findings. Also, there is a wide range of quality of the body of evidence across different health outcomes. For future studies, clear subject selection criteria and definition of "exclusive breastfeeding," reliable collection of feeding data, controlling for important confounders including child-specific factors, and blinded assessment of the outcome measures will help. Sibling analysis provides a method to control for hereditary and household factors that are important in certain outcomes. In addition, cluster randomized controlled studies on the effectiveness of various breastfeeding promotion interventions will provide further opportunity to investigate any disparity in health outcomes as a result of the intervention.

13. Jones G, Riley M, Dwyer T. Breastfeeding in early life and bone mass in prepubertal children: a longitudinal study. *Osteoporos Int.* 2000;11:146-52.
Abstract: The aim of this study was to determine whether breastfeeding in early life is associated with bone mass in prepubertal children. We studied 330 8-year-old male and female children from Southern Tasmania representing 47% of those who originally took part in a birth cohort study of risk factors for Sudden Infant Death Syndrome in 1988. Breastfeeding intention and habit were assessed in both 1988 and 1996. Bone mineral

density was measured by dual-energy X-ray densitometry. Children who were breastfed had higher bone mineral density at the femoral neck (+0.20 SD, p = 0.07), lumbar spine (+0.25 SD, p = 0.03) and total body (+0.29 SD, p = 0.006) compared with those who were bottle-fed. This association with breastfeeding was present in children born at term (femoral neck: +0.26 SD, p = 0.05; lumbar spine: +0.34 SD, p = 0.007; total body: +0.41 SD, p = 0.0008) but not those born preterm, and remained significant after adjustment for size, lifestyle factors and socioeconomic factors. Breastfeeding for less than 3 months was not associated with increased bone mass at any site. In conclusion, this study has demonstrated a beneficial association between breastfeeding in early life and bone mass in 8-year-old children born at term, particularly those breastfed for 3 months or longer, which appears biological. If this association is confirmed in other populations and persists until the attainment of peak bone mass then the implication would be that osteoporosis prevention programs need to start very early in the life cycle.

14. Kalkwarf HJ. Lactation and maternal bone health. *Adv Exp Med Biol.* 2004;554:101-14.
Abstract: Women lose bone during lactation, and this is an important mechanism to provide calcium for human milk. Bone loss during lactation occurs even in women with high calcium intakes. Lactation-induced bone loss is transient because bone density increases rapidly after weaning. Bone loss during lactation and recovery after weaning are related to ovarian function and the length of postpartum amenorrhea. The recovery of bone after weaning can occur with shortly spaced pregnancies. Women who have breastfed several infants do not have reduced bone density after menopause. Overall, the transient bone loss during lactation does not seem to increase a woman's risk of osteoporotic fracture in her elder years. Further research is needed on special subgroups of women, such as adolescents, women who are vitamin D deficient or have extremely low calcium intakes, and women who have simultaneously breastfed multiple infants to determine whether these women are able to regain sufficient bone mass after lactation to preserve their bone health.

15. Kalkwarf HJ, Specker BL. Bone mineral changes during pregnancy and lactation. *Endocrine.* 2002;17:49-53.
Abstract: Significant calcium transfer from the mother to the fetus and infant occurs during pregnancy and lactation, theoretically placing the mother at an increased risk for osteoporosis later in life. During pregnancy, intestinal calcium absorption increases to meet much of the fetal calcium needs. Maternal bone loss also may occur in the last months of pregnancy, a time when the fetal skeleton is rapidly mineralizing. The calcium needed for breast milk production is met through renal calcium conservation and, to a greater extent, by mobilization of calcium from the maternal skeleton. Women experience a transient loss of approx 3-7% of their bone density during lactation, which is rapidly regained after weaning. The rate and extent of recovery are influenced by the duration of lactation and postpartum amenorrhea and differ by skeletal site. Additional calcium intake does not prevent bone loss during lactation or enhance the recovery after weaning. The recovery of bone is complete for most women and occurs even with shortly spaced pregnancies. Epidemiologic studies have found that pregnancy and lactation are not associated with an increased risk of osteoporotic fractures.

16. Karatas M, Basaran C, Ozgul E, Tarhan C, Agildere AM. Postpartum sacral stress fracture: an unusual case of low-back and buttock pain. *Am J Phys Med Rehabil.* 2008;87:418-22.
Abstract: Low-back and buttock pain is a common complaint during pregnancy and the postpartum period and is usually attributable to mechanical lesions of the pelvis. Sacral

stress fractures are unusual but important causes that should be considered in differential diagnosis. To date, only eight postpartum sacral stress fractures have been reported in the literature. A 32-yr-old woman presented with low-back and right buttock pain that started 15 days after uneventful cesarean section delivery. Imaging studies revealed a right sacral stress fracture. Lumbar spine and femoral neck bone mineral density were normal and, except for pregnancy and lactation, no risk factors for osteoporosis were identified. There was no history of trauma, excessive weight gain, strenuous physical activity, or contribution of mechanical factors. The question remains whether this is an insufficiency fracture or a fatigue fracture. Clinicians should consider sacral fracture during pregnancy and the postpartum period as a diagnostic possibility in patients with low-back and/or buttock pain.

17. Karlsson C, Obrant KJ, Karlsson M. Pregnancy and lactation confer reversible bone loss in humans. *Osteoporos Int.* 2001;12:828-34.
Abstract: The influence of pregnancy on bone mineral density (BMD) was evaluated by dual-energy X-ray absorptiometry (DXA) in 73 women (mean age 29 years, range 20-44 years) postpartum. Fifty-five age-matched women served as controls. The influence of lactation was evaluated in 65 of the delivered women who were followed with repeated measurements, a mean of 4.5 +/- 0.1 and 11.5 +/- 0.1 months after the delivery. The influence of multiple pregnancies was evaluated in 39 premenopausal women (mean age 38 years, range 31-54 years) with a minimum of four pregnancies (range 4-7). Fifty-eight age-matched healthy premenopausal women with a maximum of two pregnancies (range 0-2) served as controls. Data are presented as mean +/- SEM. BMD data are adjusted for differences in total fat mass and total lean mass. Lumbar spine BMD was 7.6 +/- 0.1% and total body BMD 3.9 +/- 0.1% lower in women postpartum compared with controls (both $p<0.001$). BMD did not decrease significantly in non-breastfeeding mothers. Mothers breastfeeding for 1-6 months decreased femoral neck BMD by 2.0 +/- 1.0% during the first 5 months postpartum ($p<0.001$). No further BMD loss was seen between 5 and 12 months postpartum. Femoral neck BMD 12 months after delivery was 1.3 +/- 0.8% lower than after delivery in mothers breastfeeding for 1-6 months ($p = 0.05$). Mothers breastfeeding for more than 6 months decreased Ward's triangle BMD by 8.5 +/- 1.0% and lumbar spine BMD by 4.1 +/- 0.8% during the first 5 months postpartum (both $p<0.05$). No further BMD loss was seen between 5 and 12 months postpartum. Femoral neck BMD 12 months after delivery was 4.0 +/- 1.1% lower and Ward's triangle BMD 5.3 +/- 1.9% lower than after delivery in mothers breastfeeding for more than 6 months (both $p<0.05$). BMD loss was higher during the first 5 months following delivery in the lactating women compared with the non-lactating women ($p<0.05$ comparing lumbar spine BMD loss in lactating mothers versus non-lactating mothers). However, in women with a minimum of four pregnancies the BMD was no lower than in age-matched women with fewer pregnancies. Total duration of lactation was not correlated with the present BMD. In summary, pregnancy seem to confer a low BMD with additional BMD loss during 5 months of lactation. Even if complete restoration in BMD was not reached within 5 months of weaning, women with four pregnancies or more had a BMD no lower than women with two pregnancies or fewer. We conclude that neither an extended lactation period nor multiple pregnancies could be used as a risk factor when predicting women at risk for future osteoporosis.

18. Karlsson MK, Ahlborg HG, Karlsson C. Maternity and bone mineral density. *Acta Orthop.* 2005;76:2-13.
Abstract: During pregnancy and lactation, changes occur in a variety of factors which have great potential to influence bone mineral density (BMD). Smoking habits, the level of alcohol consumption, the level of physical activity, body weight, soft tissue composition and hormone levels are all factors that change during the course of these conditions. Some of these factors are capable of increasing BMD, and some can reduce it. Due to these various changes, it is virtually impossible to predict the development in BMD that will occur during a pregnancy and lactation. However, longitudinal studies have suggested that both pregnancy and lactation are associated with a BMD loss of up to 5%, albeit that the BMD recovers after weaning. Cross-sectional studies have indicated that women with many children and a long total period of lactation have similar or higher BMD and similar or lower fracture risk than their peers who have not given birth. As the studies showing this trend have been observational and cross sectional case-control studies, the conclusions can only be regarded as being suggestive, and no causality can be proven.

19. Karlsson MK, Ahlborg HG, Karlsson C. [Pregnancy and lactation are not risk factors for osteoporosis or fractures]. *Lakartidningen.* 2005;102:290-3.
Abstract: Observational and case control studies infer that a pregnancy and a period of lactation are followed by loss in bone mass of up to 5%. The reason for this loss is virtually impossible to conclude as so many factors known to influence the bone mass undergo changes during a pregnancy and lactation. The increased calcium demand, changed nutritional habits, reduced smoking and alcohol consumption seen in many women during these periods, the changes in body weight and fat content, the changed level of physical activity and the changed levels of hormones with potential to influence the bone metabolism could all influence the bone mass. Most studies also report that the deficit in "bone mass" normalises after weaning. Multiple pregnancies and long total duration of lactation cannot be regarded as risk factors for osteoporosis and fragility fractures as most reports indicate that women with multiple pregnancies have similar or higher bone mass and similar or lower fracture incidence than their peers with no children.

20. Kovacs CS. Calcium and bone metabolism during pregnancy and lactation. *J Mammary Gland Biol Neoplasia.* 2005;10:105-18.
Abstract: Pregnancy and lactation both place significant demands on the mother to provide sufficient calcium (among other minerals and nutrients) to the fetus and neonate. Despite facing similar demands for calcium during pregnancy and lactation, the maternal adaptations differ significantly between these two reproductive periods. Women lose 300 to 400 mg of calcium daily through breast milk, and this calcium demand is met by a 5-10% loss of skeletal mineral content during 6 months of exclusive lactation. Most importantly, the lost mineral is fully restored within a few months of weaning, such that women who have breastfed do not have a long-term deficit in skeletal mineral content. This article will review our present understanding of the adaptations in mineral metabolism that occur during pregnancy and lactation, and will focus on recent evidence that the breast itself plays a central role in regulating the adaptations during lactation.

21. Labbok MH. Effects of breastfeeding on the mother. *Pediatr Clin North Am.* 2001;48:143-58.
Abstract: In the rush to find nutrient alternatives to breastfeeding, a theme that dominated research on infant feeding throughout the twentieth century, only recently have new

findings that reconfirm the importance of breastfeeding for maternal and child health begun to influence medical texts and health policy. Approximately 30 years of increasingly rigorous and positive research findings have led to the rediscovery of breastfeeding as a valid and evidence-based health intervention for infants. Unfortunately, because much of the research was designed to assess human milk as a nutrient replacement for infant formula, the literature on the effects of breastfeeding on maternal health remain limited. Nonetheless, a clear pattern of positive physiologic changes that lead to improved short-term and long-term health sequelae are emerging. All patients and their families should be informed fully as to the positive preventive health effects of breastfeeding not only for infants but also for mothers. Women have many difficult choices to make; it behooves physicians to ensure that they receive all of the facts on which to base these decisions.

22. O'Sullivan SM, Grey AB, Singh R, Reid IR. Bisphosphonates in pregnancy and lactation-associated osteoporosis. *Osteoporos Int.* 2006;17:1008-12.
Abstract: INTRODUCTION: Pregnancy and lactation-associated osteoporosis (PLO) is an uncommon condition characterized by the occurrence of fracture(s) during late pregnancy or the puerperium. The aetiology is uncertain, and its management and natural history poorly defined. METHODS: We report a series of 11 women with PLO seen at our institution over the past 20 years, with follow-up ranging from 1 to 19 years. RESULTS: Ten women presented with painful low-trauma vertebral fractures, at a median of 1 month postpartum. In nine cases the fractures were multiple (median: 3, range: 2-5). At least one recognised risk factor for osteoporosis (low body weight, smoking history, family history of osteoporosis/fracture, vitamin D insufficiency) was present in nine patients. Bone density was in the osteoporotic range at the spine (mean T score: -2.8), with less marked reduction at the proximal femur (mean T score: -1.9). Nine patients received bisphosphonate treatment, for a median duration of 24 months. In the five women who received a bisphosphonate within 1 year of presentation, spinal bone density increased by 23% over baseline values after 2 years of treatment (p=0.0014). Of the 5 women who had subsequent pregnancies, one, who had declined bisphosphonate therapy after the initial presentation, sustained a fracture in the postpartum period. Two patients (both of whom were followed for at least 10 years) sustained fractures outside of pregnancy. CONCLUSIONS: PLO is therefore associated with significant morbidity, a high prevalence of recognized risk factors for osteoporosis and a risk of recurrence in subsequent pregnancies. Bisphosphonate therapy administered soon after presentation substantially increases spinal bone density in patients with PLO.

23. Ofluoglu O, Ofluoglu D. A case report: pregnancy-induced severe osteoporosis with eight vertebral fractures. *Rheumatol Int.* 2008;29:197-201.
Abstract: Osteoporosis associated with pregnancy and lactation is a rare condition. The prevalence, etiology and its pathogenesis is unknown. It causes one or more vertebral fractures with severe, prolonged back pain and height loss in affected women. Majority of the cases are seen in the third trimester or just after delivery in primagravid women. In this case report, a 30-year-old woman who had severe pregnancy-induced osteoporosis with 8 vertebral fractures was presented. During last month of her first pregnancy she had moderate back pain. After delivery, the back pain has gotten worse. The radiological examinations have shown that there was 50% in T(6), T(8) and T(10); 30% in L(2); 20% in L(1) height loss and biconcave vertebral images in L(3-5). In the bone mineral density, L(2-4) T score was -4.7 and total femoral T score was -3.1. There was no abnormality in the laboratory findings except mild elevation in alkaline phosphates. Although pregnancy-

associated osteoporosis is a rare condition, when pain occurs in the last trimester or early postpartum period, it should be considered in differential diagnosis.

24. Pearson D, Kaur M, San P, Lawson N, Baker P, Hosking D. Recovery of pregnancy mediated bone loss during lactation. *Bone.* 2004;34:570-8.
Abstract: It is uncertain whether bone is routinely mobilised during pregnancy to provide calcium for the fetus and whether this is of a magnitude to cause osteoporosis. We have made sequential measurements of lumbar spine and hip bone mineral density (BMD) in 60 normal women before conception and then during the subsequent pregnancy out to one year after delivery. During pregnancy there was a significant fall in the BMD at the spine (1.53%), total hip (1.15%), and trochanter (3.90%) but not at the femoral neck. After delivery the women who breast-fed (n=34) showed a significant fall in BMD at all measurement sites (P<0.001) with the greatest change at the spine (4.7 +/- 3.1%) with 38% of women showing a change >5%. The women who bottle fed (n=10) increased or maintained BMD at all sites with the mixed feeders (n=16) showing an intermediate response. There was no consistent relationship between the change during pregnancy and lactation but 47% of the breast-feeders lost >5% at either the lumbar spine or trochanter. There was a good correlation between the change in BMD at these two sites (r=0.48, P<0.001). At 1 year after delivery all but 7 women had returned to within 5% of the preconceptual value at the spine and trochanter but the recovery at the total hip was less complete. Several women became transiently osteoporotic (T score below -2.5) at either spine or hip during reproduction of whom three started pregnancy with a normal BMD.

25. Rea MF. [Benefits of breastfeeding and women's health]. *J Pediatr (Rio J).* 2004;80:S142-6.
Abstract: OBJECTIVE: To review breastfeeding benefits for the women's health. SOURCES OF DATA: Lilacs, MEDLINE, SciELO, BIREME, Cochrane Library and Google were searched for the keywords: breastfeeding and breast cancer, ovarian cancer, osteoporosis, rheumatoid arthritis, lactation amenorrhea, post natal period, and women's health. Single articles published between 1990 and 2004 were considered, as well as remarkable ones prior to this period. SUMMARY OF THE FINDINGS: There are a few articles published on the topic, even though, the existing literature reveals that there is a positive relationship between breastfeeding and decreased risk of breast cancer, cancer of the ovarian epithelium, and osteoporosis leading to hip fracture. Some studies suggest the effect of breastfeeding on the decreasing risk of rheumatoid arthritis, others mention the relation between breastfeeding and faster loss of weight gained during the gestational period. Several studies show how breastfeeding interferes on the onset of postnatal menstruation and consequent birth spacing. CONCLUSIONS: Breastfeeding provides important benefits for the women's health, such as reduced risk of breast and ovarian cancer, decreased risks of hip fractures and contribution to the increase of birth spacing.

26. Ruiz-Irastorza G, Khamashta MA, Hughes GR. Heparin and osteoporosis during pregnancy: 2002 update. *Lupus.* 2002;11:680-2.
Abstract: Although significant bone mass loss is rare during pregnancy, some situations may increase the risk of symptomatic osteoporosis. Heparin may be necessary for a number of pregnant women with systemic lupus erythematosus and antiphospholipid syndrome. The osteopenic effect of heparin is low even during pregnancy, and recent data point to a more favourable profile of low-molecular-weight heparins as compared with unfractionated

heparin. Lactation results in a significant increase of calcium demands and may be a higher risk period for women at risk for osteoporosis.

27. Sarli M, Hakim C, Rey P, Zanchetta J. [Osteoporosis during pregnancy and lactation]. *Medicina (B Aires).* 2005;65:533-40.
Abstract: During pregnancy and lactation women have to form and maintain fetus and newborn skeleton. These processes require maternal hormonal and metabolic adjustments. During the first weeks of pregnancy, calcium intestinal absorption rise and reach a maximum in the last trimester. Hypercalciuria can be detected until lactation is stopped. During lactation, calcium that is present in maternal milk, results from lowering maternal calcium excretion and increasing bone resorption. Plasma 1,25 (OH)(2) D(3) levels increase two-fold early in pregnancy due to high placental 1-alpha-hydroxilase activity, remain high until delivery and decline to normal values during lactation. Estrogen, prolactin and placental lactogen, which are involved in calcium absorption, increase at the same time. Normal or even low levels of parathyroid hormone (PTH) can be detected during pregnancy. This suggests that their physiological actions could be mimicked by the parathyroid- related-peptide (PTHrP), which increases in late stages of pregnancy and remain high during delivery and lactation. Calcitonin levels increase during pregnancy, decline during lactation and return to normal values after lactation is stopped. The physiological roll of tumor necrosis factor, interleukin 6 and osteoprotegerin has not been elucidated yet. The above mentioned changes can exceptionally lead to generalized or regional osteoporosis. The aim of this article is to review the published bibliography concerning the physiopathology of these diseases.

28. Sarli M, Hakim C, Rey P, Zanchetta J. [Osteoporosis during pregnancy and lactation. Report of eight cases]. *Medicina (B Aires).* 2005;65:489-94.
Abstract: Both generalized and regional osteoporosis exceptionally occur during pregnancy and lactation. The aim of this paper is to show our experience in the diagnosis and treatment of these diseases. From 1984 to 2004 six lactating women with osteoporosis and two with regional osteoporosis consulted us. In the former group, three patients had vertebral fractures and the others experienced substantial demineralization detected by dual-energy X-ray absorptiometry (DXA). In all cases, symptoms began during the third trimester of pregnancy or immediately after delivery. Five of them were primiparous and one was multiparous with a long period of lactation. Risk factors were: low calcium intake, low weight, family history of osteoporosis, amenorrhea, cigarette consumption and corticosteroid therapy. Laboratory tests evidenced increased bone turnover. DXA scan showed substantial demineralization, particularly in axial skeleton. Lactation was interrupted in all women and four received anti-resorptive drugs, one estrogen and only calcium plus vitamin D the remaining. All of them, but one, evolved successfully. The women affected by regional osteoporosis complained of unilateral pain and progressive functional limitation of right foot and left hip respectively. Reduced bone mineral density at symptomatic sites was seen by DXA. Diagnosis was confirmed by typical magnetic resonance imaging pattern. Both patients cured with rest and bisphosfonates treatment.

29. Sekhar RV, Vassilopoulou-Sellin R. Interplay of pregnancy, lactation, and hyperthyroidism leading to severe osteoporosis in a young woman. *Endocr Pract.* 2001;7:262-6.
Abstract: OBJECTIVE: To describe the case of a young woman who had severe osteoporosis due to the compounding effects of pregnancy, lactation, and hyperthyroidism and who had a presumed metastatic lesion in the lumbar spine. METHODS: We present the

clinical, pathologic, radiologic, and laboratory findings and describe the clinical course of our patient. RESULTS: A 31-year-old Arabic woman was referred to the M. D. Anderson Cancer Center because of a lytic lesion in her lumbar spine, presumed to be metastatic deposits. She had a history of two consecutive pregnancies and intermittently treated hyperthyroidism. Our initial evaluation revealed that the patient had clinical and biochemical thyrotoxicosis, and we treated her with thionamides, corticosteroids, and radioiodine ablation. Radiologic studies disclosed a complex renal cyst that had increased uptake on a bone scan, which was highly suggestive of a primary malignant lesion. Ultimately, however, it proved benign on pathologic analysis after a left nephrectomy. Bone mineral density measurements identified severe osteoporosis (T-scores: lumbar spine, -3.3; right hip, -2.2; and left hip, -2.0), which had led to vertebral collapse and was misinterpreted as malignant metastatic disease. The bone mineral densities improved (+5 to +11% at the various sites) within 4 months after definitive treatment and cure of the hyperthyroidism. CONCLUSION: The effect of pregnancies and prolonged lactation, in the milieu of other risk factors for bone depletion such as hyperthyroidism, may cause severe osteoporosis in a young patient. The resulting osteoporosis may manifest as a lesion suggestive of malignant metastatic involvement.

30. Stumpf UC, Kurth AA, Windolf J, Fassbender WJ. Pregnancy-associated osteoporosis: an underestimated and underdiagnosed severe disease. A review of two cases in short- and long-term follow-up. *Adv Med Sci.* 2007;52:94-7.
Abstract: Pregnancy-associated osteoporosis is an uncommon condition characterized by the occurrence of painful fractures during late pregnancy or lactation. To date the pathophysiology of this entity of bone disorder is still uncertain, and its therapeutical management is poorly defined. We report two clinical cases: a 10-years follow-up with pain medication and intermittent antiresorptive therapy courses, subsequent traumatic vertebral fracture and actually fracture of scaphoid after inadequate trauma. Beside this long-term course a young female patient with pregnancy-associated osteoporosis and painful lumbar and also thoracic vertebral fractures is described. She was treated with an osteoanabolic therapy, at the timepoint of first follow-up at 6 months of treatment a solid increase of bone mineral density and sustained pain reduction was observed.

31. Tran HA, Petrovsky N. Pregnancy-associated osteoporosis with hypercalcaemia. *Intern Med J.* 2002;32:481-5.
Abstract: Pregnancy-associated osteoporosis is an uncommon condition. It predominantly affects thinly built, primigravid, lactating women. These patients can sustain vertebral fractures with minimal or no trauma, resulting in significant morbidity. The association with hypercalcaemia is rare and typically occurs during the first few months postpartum, while lactating. This condition is, however, relatively benign and patients can expect to return to normal bone mineral density 6-12 months after breast-feeding has stopped.

32. Weisman SM. The calcium connection to bone health across a woman's lifespan: a roundtable. *J Reprod Med.* 2005;50:879-84.
Abstract: Adequate calcium throughout a woman's lifespan is a critical step to achieving and improving bone health. Unfortunately, there is no time across this continuum where the average intake is optimal. This paper reviews the output of a roundtable of scientific professionals who gathered to discuss approaches for turning high levels of awareness regarding the importance of adequate calcium intake into behaviors that actualize this recognition throughout the life of a woman. The critical time periods of pregnancy,

lactation, perimenopause and menopause, in which adequate calcium intake is most important, are particularly highlighted. Recommended levels of calcium and vitamin D are reviewed with emphasis on diet and supplemental sources of these nutrients. Knowledge of the current shortfall in calcium intake across the life continuum coupled with health care professional education about the importance of compliance with recommendations will increase calcium awareness and utilization and improve bone health.

33. Yamaga A, Taga M, Takahashi T, Shirai T. A case of postpregnancy osteoporosis. *Eur J Obstet Gynecol Reprod Biol.* 2000;88:107-9.
Abstract: A puerperant woman, who was previously healthy and had no disease known to affect bone metabolism, experienced lower back pain and lumbar vertebral fractures during lactation. Both bone formation markers and resorption markers were markedly elevated. Bone mineral density of the lumbar spine as measured by dual energy X-ray absorptiometry was extremely low. She stopped lactation through the use of bromocriptine because of the large volume of milk secretion. After treatment with calcitonin injections and the use of a corset, her back pain gradually disappeared. This case appears to be postpregnancy osteoporosis.

34. Yoon BK, Lee JW, Choi DS, Roh CR, Lee JH. Changes in biochemical bone markers during pregnancy and puerperium. *J Korean Med Sci.* 2000;15:189-93.
Abstract: To elucidate the changes in bone turnover during pregnancy and puerperium, we measured serially the levels of serum osteocalcin and urine deoxypyridinoline (Dpy) as markers of bone formation and bone resorption, respectively, in 22 healthy women with normal pregnancy. Nineteen non-pregnant women served as control. The Dpy levels increased significantly at 16 weeks of pregnancy and remained elevated thereafter. The levels of osteocalcin, however, were significantly decreased at 16 weeks of pregnancy and elevated later at 6 weeks postpartum. Bone turnover ratio (Dpy/osteocalcin) continued to rise during pregnancy, but returned to control levels 6 weeks after delivery. Dpy levels and bone turnover ratio during puerperium tended to be higher in 17 breast-feeding women than those of 5 exclusive bottle-feeders. In conclusion, bone resorption begins to increase from the second trimester of pregnancy and calcium release from bone tissue might play a major role in calcium homeostasis during the whole period of pregnancy as well as during lactation.