THE EFFECT OF MULTIPLE PREGNANCIES AND LACTATION ON BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN

POSTMENAPOZAL KADINLARDA GEBELİK SAYISI VE LAKTASYONUN KEMİK MİNERAL DANSİTESİ ÜZERİNE ETKİLERİ

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ABSTRACT

Purpose: *Pregnancy and lactation are the two stages of life that cause changes in the calcium and bone metabolism. This study was designed to evaluate the effect of multiple pregnancies and lactation on the bone mineral density (BMD) of postmenopausal women.* ***Methods:*** *Ninety-nine normal weight, non-smoking postmenopausal women without a history of immobilization and drugs affecting BMD were included in the study. The subjects were grouped according to the number of pregnancies (group 1 included 1-4 pregnancies, group 2 included 5-9 and group 3 included ≥10) and total duration of lactation (≤20 months as group 1, 20-60 months as group 2 and >60 months as group 3). Total duration of menses was calculated for each subject. Bone density of the lumbar vertebrae 1-4 (L1-4), femoral neck, Ward's triangle and trochanter regions were measured with dual energy X-ray absorptiometry.* ***Results:*** *An increased number of pregnancies caused lower BMD in the spine, but the duration of lactation has no effect on the BMD of any site and the total duration of menstruation also had no effect on BMD in the postmenopausal period.* ***Conclusion:*** *Subsequent pregnancies without a sufficient interval in between may cause insufficient mineral replacement in maternal tissues and predispose the woman to osteoporosis.*

Key Words: *1. Lactation, 2. Pregnancy, 3. Osteoporosis.*

ÖZET

Amaç: *Gebelik ve laktasyon hayatın, kalsiyum ve kemik metabolizmasında değişikliklere neden olan iki dönemidir. Bu çalışma postmenapozal kadınlarda gebelik sayısı ve laktasyonun kemik mineral dansitesi (KMD) üzerine etkisini araştırmak için planlanmıştır.* ***Metod:*** *Normal vücut ağırlığında, sigara içmeyen, immobilizasyon veya osteoporoza neden olacak ilaç öyküsü olmayan 99 postmenapozal kadın çalışmaya alındı. Olgular gebelik sayılarına (1-4 gebelik öyküsü olanlar grup 1, 5-9 gebelik grup 2, ≥ 10 gebelik grup 3) ve toplam laktasyon sürelerine (≤20 ay grup 1, 20-60 ay grup 2, > 60 ay grup 3) göre gruplandırıldı. Her olgu için toplam menstruasyon süresi hesaplandı. Lomber vertebra 1-4 (L1-4), femur boynu, ward's üçgeni ve trokanterik bölgede kemik dansitesi dual enerji X-ray absorbsiyometri ile ölçüldü.* ***Bulgular:*** *Artmış gebelik sayısının vertebralarda KMD'de azalmaya neden olabileceği, fakat toplam laktasyon süresinin hiçbir bölgede KMD üzerine bir etkisi olmadığı ve toplam menstruasyon süresinin postmenapozal dönemde KMD'yi etkileyen bir faktör olmadığı tesbit edilmiştir.* ***Sonuç:*** *Aralarında yeterli süre bulunmayan ardarda olan gebelikler, maternal dokularda yetersiz mineral replasmanına neden olarak osteoporoz gelişimine zemin hazırlıyor olabilir.*

Anahtar Kelimeler: *1. Laktasyon, 2. Gebelik, 3. Osteoporoz.*

INTRODUCTION

Pregnancy and lactation are the two stages in a woman's life that are characterized by hormonal changes. These changes raise the question as to whether these stages have any effect on bone mineral density (BMD). Due to bone mineralization in the fetus and as the neonate needs calcium, a 3-10% drop and regain of bone density in the woman can be seen during these periods (1). During pregnancy, the increased calcium need of the fetus can be met mainly by increased maternal intestinal calcium absorption and decreased renal calcium losses and to a lesser extent by increased calcium

Table- 1: Clinical characteristics of the subjects grouped according to the number of pregnancies.

	Group 1	Group 2	Group 3	P
BMI	25.2 ± 2.3	25.8 ± 2.7	26 ± 2.1	>0.05
Age	55.7 ± 6.3	58.8 ± 6.6	60.6 ± 4.5	>0.05
Duration of menstrual period	30.3 ± 5.5	32.8 ± 7	32.9 ± 5.5	>0.05
Duration of lactation	26.1 ± 28.9	53.9 ± 34.3	108.7 ± 63.9	<0.01

Values are given as the mean ± standard deviation.

Table- 2: Clinical characteristics of the subjects grouped according to the duration of lactation.

	Group 1	Group 2	Group 3	P
Age	57.8 ± 6.1	57.7 ± 7.1	60.5 ± 4.7	>0.05
BMI	24. 8 ± 2.3	25.7 ± 2.5	26.3 ± 2.2	>0.05
Parity	3.4 ± 2.0	5.9 ± 3.9	7.8 ± 3.6	<0.01
Duration of menstrual period	30.2 ± 5.9	31.7 ± 6.4	33.7 ± 5.9	>0.05

Values are given as the mean ± standard deviation.

Table- 3: Results of DEXA (BMD) in the subjects grouped according to the number of pregnancies.

	Group 1	Group 2	Group 3	P
N	44	38	17	
L_{1-4} (g/cm²)	0.7977±0.10	0.7545±0.10	0.7059±0.10	0.044
Femoral neck (g/cm²)	0.7945±0.99	0.6408±0.09	0.6366±0.10	0.561
Trochanteric region (g/cm²)	0.5139±0.08	0.5219±0.08	0.4855±0.06	0.429
Ward's triangle (g/cm²)	0.5131±0.10	0.4882±0.09	0.4806±0.10	0.522

Values are given as the mean ± standard deviation.

Table- 4: Results of DEXA (BMD) in the subjects grouped according to the duration of lactation.

	Group 1	Group 2	Group 3	P
N	34	35	30	
L_{1-4} (g/cm²)	0.7849±0.10	0.7707±0.10	0.7459±0.10	0.470
Femoral neck (g/cm²)	0.6230±0.10	0.6550±0.09	0.9252±1.30	0.212
Trochanteric region (g/cm²)	0.4984±0.07	0.5355±0.08	0.5050±0.08	0.139
Ward's triangle (g/cm²)	0.4896±0.10	0.5210±0.10	0.4811±0.10	0.347

Values are given as the mean ± standard deviation.

resorbtion from the maternal skeleton (1,2). However, during lactation, the maternal skeleton is the main source for the calcium need of the neonate (3-5). The purpose of this study is to determine whether the BMD of postmenopausal women is affected by the number of pregnancies and the total duration of lactation.

MATERIALS AND METHODS

Among the women admitted to the osteoporosis clinic, 187 healthy postmenopausal women completed a questionnaire covering medical and reproductive histories. Women who were smoking, obese (body mass index ≥30) or underweight (body mass index <18.5), over 65 years of age and who had a history of immobilization history or of drugs affecting BMD such as glucocorticoids were excluded. The remaining 99 postmenopausal women who fulfilled the criteria were included in the study. The subjects were grouped according to the number of completed pregnancies (1-4 pregnancies in group 1, 5-9 pregnancies in group 2, ≥10 pregnancies in group 3) and the total duration of lactation (< 20 months in group 1, 20-60 months in group 2, >60 months in group 3). The total duration of menses was also calculated for each patient. The BMDs of lumbar vertebrae 1-4 (L1-4), femoral neck, Ward's triangle and trochanter regions were measured with dual energy X-ray absorptiometry (DEXA).

The statistical analysis of data was performed by one-way ANOVA and correlation tests.

Results are given as mean ± standard deviation.

RESULTS

Mean age in the groups 1, 2 and 3 according to the number of pregnancies was 55.7 ± 6.3 years (range: 44-65 years), 58.8 ± 6.6 years (range: 44-65 years) and 60.6 ± 4.5 years (range: 50-65 years), respectively. The patients grouped according to the total duration of lactation had a mean age of 57.8 ± 6.1 years (range: 44-65 years), 57.7 ± 7.1 years (range: 44-65 years) and 60.5 ± 4.7 years (range: 49-65) in groups 1, 2 and 3, respectively. The clinical characteristics of the groups are shown in detail in Tables 1 and 2. We found that an increased number of pregnancies was associated with decreased BMD in the lumbar region but no effect of pregnancy was seen at other sites. There was no association between BMD and the total duration of lactation or menses. The BMD measurements at various sites according to the number of pregnancies and duration of lactation are shown in Tables 3 and 4, respectively.

DISCUSSION

Skeletal adaptation is a complex event affected by nutritional, environmental and physiological factors. Pregnancy and lactation, which are the two main reproductive cycles, are also suspected to affect BMD.

In the literature, there are conflicting results related to the effect of pregnancy and lactation on BMD. We found that an increased number of pregnancies is associated with lower BMD at the lumbar spine, but the duration of lactation does not have a clinically important effect on BMD during postmenopausal life and the total duration of menstruation is not a predictor of BMD status.

There are other studies supporting our finding that pregnancy causes an approximately 2% decrease in BMD, especially at the lumbar spine (6-10). Black et al reported a mean reduction in spinal BMD of 3.5% in the 9 months from prepregnancy to the immediate postpartum period (8). Drinkwater and Chesnut showed that lumbar BMD decreased 3.3% during pregnancy but returned to prepregnancy values during lactation, while bone loss at the femoral neck continued during lactation (11). Some follow-up studies show that pregnancy causes mineral loss, but during or after a certain duration of lactation and resumption of menses it recovers (9,10). Lactation may have a protective role or the cessation of lactation may be a trigger for a bony replacement process. It is known that during lactation the basal concentration of prolactin is high and estrodiol level is low (12), which can lead to osteoporosis. The cessation of lactation restores these hormones to normal levels and may start recovery.

In contrast to our results, Grainge et al found that pregnancy causes an increase in BMD at the femoral neck and total radius (13). However, they could not show a positive effect on the spine, trochanter or total body and they also reported, in parallel to our findings, that no association was present between the total duration of breast-feeding and BMD at any site. In a study including perimenopausal women aged between 40 and 54, those with a lactation history were found to have a higher lumbar BMD compared to those without such a history, but no significant increase was detected at the mid- or distal radius (14). Lamke et al showed that pregnant women exhibit a loss in trabecular bone but not in cortical bone (15). They also found that while lactation shorter than 3 months causes mineral loss during the first 3 months, nursing for longer than 3 months does not cause mineral loss and suggested that nursing for a longer period may play a protective role. A positive relationship between parity and bone mass was reported by Murphy et al (16). Fox et al found that a 1.4% increase in distal radius bone density was observed with each additional birth, but they did not investigate the spine or hip (17). Sowers et al demonstrated that fetal demand for calcium has a minimal effect on BMD at parturition (18).

Besides these conflicting results, Koetting and Wardlaw could not find a relation between a history of long-term lactation and bone density (19). Hadji et al (20) and Karlsson et al (21) suggested that neither parity nor breast feeding could be used as risk factors for osteoporosis. It was also reported that the negative effect of pregnancy and lactation on the maternal bone mass was spontaneously compensated for after weaning (10). In another study, conducted in a group of women who were pregnant or lactating during most of their adult reproductive lives due to their religious beliefs, it was shown that multiple pregnancies followed by lactation

without a recovery interval are not associated with lowered BMD (22). In the literature there are some reports of fractures during puerperium due to pregnancy-associated osteoporosis (23-27). The actual incidence is unknown and although it seems to be idiosyncratic (28) its pathogenesis is still obscure. Even in these cases, the recovery of BMD after pregnancy and especially following the cessation of lactation was reported.

Grainge et al pointed out the importance of the total duration of menses (13). They reported that years of menstruation is a good predictor of BMD. Fox et al showed that women with earlier menarche, longer menstruation and longer total duration of menses had greater distal radius bone density (17). However, we could not find either a negative or positive association between total duration of menses and BMD.

The bony changes during pregnancy and lactation and the causative factors for these changes are still under investigation. Parathyroid hormone-related peptide (PTHrP) is one of these factors. It originates from the placenta and is suggested to contribute to the maintainance of the fetal-maternal calcium gradient (29,30). It is found that PTHrP may induce uncoupled bone turnover with decreased cortical bone formation (31). It is also elevated during the postgestational period, but its effect on the calcium metabolism during lactation has been found to be weak and temporary. Therefore, it is suggested that PTHrP does not seem to participate significantly in the regulation of bone turnover during lactation (32). Its role seems greater, however, because different parathyroid hormone (PTH) receptors are identified and cloned, and the almost ubiquitous distribution of PTHrP and PTH/PTHrP receptor (33) suggests the existence of other PTH-related receptors in the body and a much greater complexity of the bone and mineral metabolism. Factors such as pre-pregnancy BMI, weight gain, dietary calcium intake, physical activity, diabetes mellitus and hypertension during pregnancy and correlation with baby weight and height were also investigated. Although pre-pregnancy BMI and weight gain during pregnancy could not be linked with changes in BMD, the women with greater bone density and nulliparous women were demonstrated to have a greater extent of loss postpartum (34,35). Sowers et al showed that pregnancy during adolescence causes bone loss more than that during adult life (35). Pregravid weight, gynecological age, age at menarch, greater dietary intake, less physical activity, and pregnancy hypertension and preeclampsia were found to be not related to bone change (35). A previous study using the single photon absorptiometry method for radial bone mineral content assessment reported low bone mass in infants of diabetic mothers compared to control subjects (36). However, it is shown by using dual X-ray absorptiometry, which is accepted as an accurate and precise noninvasive technique for assessing bone mineralization, that bone mineralization and fat mass are increased at birth in infants of diabetic mothers compared to reference curves (37). Infants of diabetic mothers are hyperinsulinemic and hyperinsulinemia causes a marked stimulation of bone matrix synthesis and cartilage formation (37). Insulin also increases insulin-like growth factor production by the liver, which enhances bone collagen and matrix synthesis and stimulates the replication of cells of the osteoblast lineage (37). It is suggested that there is an increase in bone formation in pregnant women with type 1 diabetes that may be related to the increased amount of insulin administered and the improvement in diabetic control associated with pregnancy (38). Postpartum bone mineral density showed a significant, positive correlation with baby weight and height (34).

Although preeclampsia is reported not to be associated with bone changes, calcium supplementation was associated with an approximately 50% decrease in the risk of all types of pregnancy-induced hypertension (39,40). Calcium supplementation during the third trimester of pregnancy and vitamin D supplementation during the 27th and 32nd amenorrhea weeks in winter are also reported to reduce bone resorbtion and prevent hypocalcemia respectively (41,42). Breast-milk calcium concentration and hence the calcium intake of the breast-fed infant may be influenced by maternal calcium intake during the preceding pregnancy, but there are also studies suggesting that the changes in the calcium and bone metabolism of the mother and infant that accompany lactation are independent of the current calcium intake (43). It is thought that there must be hormonal mechanisms other than PTH/PTHrP, calcitonin

and 1,25 dihydroxyvitamin D, as yet unidentified, involved in regulating the homeorrhetic changes in the calcium and bone metabolism associated with pregnancy and lactation (43).

Subsequent pregnancies without a sufficient interval in between may cause insufficient mineral replacement in maternal tissues and predispose the woman to osteoporosis. The difference between the results of our study and some of the other studies in the literature may be due to the different ethnic groups, eating habits and attitudes during parturition of the study populations. The exact effect of pregnancy and lactation can be determined by a study performed in larger populations including different ethnic groups and in populations with different dietary habits and life styles. An understanding of the recovery mechanism after the cessation of lactation and the underlying causes leading to different results in these studies may be very important when considering the future therapy of osteoporosis.

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REFERENCES

1. Kovacs CS. Calcium and bone metabolism in pregnancy and lactation. J Clin Endocrinol Metab 2001; 86: 2344-2348.
2. 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: 189-193.
3. Morgan SL. Calcium and vitamin D in osteoporosis. Rheum Dis Clin North Am 2001; 27: 101-130.
4. Ensom MH, Liu PY, Stephenson MD. Effect of pregnancy on bone mineral density in healthy women. Obstet Gynecol Surv 2002; 57: 99-111.
5. Sowers M. Premenopausal reproductive and hormonal characteristics and the risk for osteoporosis. In. Marcus R, Feldman D, Kelsey J (eds): Osteoporosis, San Diego, Academic Press; 1996. p. 529-549.
6. Smith R, Athanasou NA, Ostlere SJ, Vipond SE. Pregnancy associated osteoporosis. Q J Med 1995; 88: 865-878.
7. Khovidhunkit W, Epstein S. Osteoporosis in pregnancy. Osteoporos Int 1996; 6: 345-354.
8. Black AJ Topping J, Durham B, Farquharson RG, Fraser WD. A detailed assessment of alterations in bone turnover, calcium homeostasis, and bone density in normal pregnancy. J Bone Miner Res 2000; 15: 557-563.
9. Holmberg-Marttila D, Sievänen H, Laippala P, Tuimala R. Factors underlying changes in bone mineral during postpartum amenorrhea and lactation. Osteoporos Int 2000; 11: 570-576.
10. More C, Bettembuk P, Bhattoa HP, Balogh A. The effects of pregnancy and lactation on bone mineral density. Osteoporos Int 2001; 12: 732-737.
11. Drinkwater BL, Chesnut CH 3rd. Bone density changes during pregnancy and lactation in active women: a longitudinal study. Bone Miner 1991; 14: 153-160.
12. Baird DT, McNeilly AS, Sawers RS, Sharpe RM. Failure of estrogen-induced discharge of luteinizing hormone in lactating women. J Clin Endocrinol Metab 1979; 49: 500-506.
13. Grainge MJ, Copland AC, Cliffe SJ, Chilvers CED, Hosking DJ. Reproductive, menstrual and menopausal factors: which are associated with bone mineral density in early postmenopausal women? Osteoporos Int 2001; 12: 777-787.
14. Feldblum PJ, Zhang J, Rich LE, Fortney JA, Talmage RV. Lactation history and bone mineral density among perimenopausal women. Epidemiology 1992; 3: 527-531.
15. Lamke B, Brundin J, Moberg P. Changes of bone mineral content during pregnancy and lactation. Acta Obstet Gynecol Scand 1977; 56: 217-219.
16. Murphy S, Khaw KT, May H, Compston JE. Parity and bone mineral density in middle-aged women. Osteoporos Int 1994; 4: 162-166.
17. Fox KM, Magaziner J, Sherwin R, Scott JC, Plato CC, Nevitt M, Cummings S. Reproductive correlates of bone mass in older women. J Bone Miner Res 1993; 8: 901-908.
18. Sowers M, Crutchfield M, Jannausch M, Updike S, Corton G. A prospective evaluation of bone mineral change in pregnancy. Obstet Gynecol 1991; 77: 841-845.
19. Koetting CA, Wardlaw GM. Wrist, spine and hip bone density in women with variable histories of lactation. Am J Clin Nutr 1988; 48: 1479-1481.
20. Hadji P, Ziller V, Kalder M, Gottschalk M, Hellmeyer L, Hars O, Schmidt S, Schulz KD. Influence of pregnancy and breast-feeding on quantitative ultrasonometry of bone in postmenopausal women. Climacteric 2002; 5: 277-285.
21. Karlsson C, Obrant KJ, Karlsson M. Pregnancy and lactation confer reversible bone loss in humans. Osteoporos Int 2001; 12: 828-834.
22. 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: 1371-1377.

23. Sekhar RV, Vassilopoulou-Sellin R. Interplay of pregnancy, lactation and hyperthyroidism leading to severe osteoporosis in a young woman. Endocr Pract 2001; 7: 262-266.
24. Yamaga A, Taga M, Takahashi T, Shirai T. A case of postpregnancy osteoporosis. Eur J Obstet Gynecol Reprod Biol 2000; 88: 107-109.
25. Liel Y, Atar D, Ohana N. Pregnancy-associated osteoporosis: preliminary densitometric evidence of extremely rapid recovery of bone mineral density. South Med J 1998; 91: 33-35.
26. Anai T, Tomiyasu T, Arima K, Miyakawa I. Pregnancy-associated osteoporosis with elevated levels of circulating parathyroid hormone-related protein: a report of two cases. J Obstet Gynaecol Res 1999; 25: 63-67.
27. Funk JL, Shoback DM, Genant HK. Transient osteoporosis of the hip in pregnancy: natural history of changes in bone mineral density. Clin Endocrinol (Oxf) 1995; 43: 373-382.
28. Kaur M, Pearson D, Godber I, Lawson N, Baker P, Hosking D. Longitudinal changes in bone mineral density during normal pregnancy. Bone 2003; 32: 449-454.
29. Glerean M, Plantalech L. Osteoporosis in pregnancy and lactation. Medicina (B Aires) 2000; 60: 973-981.
30. Lafond J, Goyer-O'Reilly I, Laramee M, Simoneau L. Hormonal regulation and implication of cell signaling in calcium transfer by placenta. Endocrine 2001; 14: 285-294.
31. Torring O, Turner RT, Carter WB, Firek AF, Jacobs CA, Health H 3rd. Inhibition by human interleukin-1 alpha of parathyroid hormone-related peptide effects on renal calcium and phosphorus metabolism in the rat. Endocrinology 1992; 131: 5-13.
32. Dobnig H, Kainer F, Stepan V, Winter R, Lipp R, Schaffer M, Kahr A, Nocnik S, Patterer G, Leb G. Elevated parathyroid hormone-related peptide levels after human gestation: relationship to changes in bone and mineral metabolism. J Clin Endocrinol Metab 1995; 80: 3699-3707.
33. Urena P. The PTH/PTHrP receptor: biological implications. Nefrologia 2003; 23 (suppl 2): 12-17.
34. Yoneyama K, Ikeda J. Change in maternal bone mineral density during pregnancy and relationship between the density and foetus growth-a prospective study. Nippon Koshu Eisei Zasshi 2000; 47: 661-669.
35. Sowers MF, Scholl T, Harris L, Jannausch M. Bone loss in adolescent and adult pregnant women. Obstet Gynecol 2000; 96: 189-193.
36. Mimouni F, Steichen JJ, Tsang RC, Hertzberg V, Miodovnik M. Decreased bone mineral content in infants of diabetic mothers. Am J Perinatol 1988; 5: 339-343.
37. Lapillonne A, Guerin S, Braillon P, Claris O, Delmas PD, Salle BL. Diabetes during pregnancy does not alter whole body bone mineral content in infants. J Clin Endocrinol Metab 1997; 82: 3993-3997.
38. Ogueh O, Khastgir G, Studd J, Jones J, Alaghband-Zadeh J, Johnson MR. Increased maternal bone formation in type I diabetic pregnancies. Calcif Tissue Int 1999; 65: 211-213
39. Hojo M, August P. Calcium metabolism in preeclampsia: supplementation may help. Medscape Womens Health 1997; 2: 5.
40. Wanchu M, Malhotra S, Khullar M. Calcium supplementation in pre-eclampsia. J Assoc Physicians India 2001; 49: 795-798.
41. Janakiraman V, Ettinger A, Mercado-Garcia A, Hu H, Hernandez-Avila M. Calcium supplements and bone resorption in pregnancy: a randomized crossover trial. Am J Prev Med 2003; 24: 260-264.
42. Madelenat P, Bastian H, Menn S. Winter supplementation in the 3rd trimester of pregnancy by a dose of 80,000 IU of vitamin D. J Gynecol Obstet Biol Reprod 2001; 30: 761-767.
43. Prentice A. Maternal calcium metabolism and bone mineral status. Am J Clin Nutr 2000; 71: 1312S-1316S.