Dietary calcium and pregnancy-induced hypertension: is there a relation?[1–3]

Lorrene D Ritchie and Janet C King

ABSTRACT The evidence that calcium plays a role in the etiology, prevention, and treatment of pregnancy-induced hypertension (PIH) is reviewed. The precise factors involved in the pathogenesis of PIH are unclear, but several alterations in calcium metabolism have been identified. Epidemiologic data suggest an inverse correlation between dietary calcium intake and incidence of PIH. Although evidence suggests a possible beneficial effect of supplemental calcium, contradictions persist in clinical trials of pregnant women. Presently, there is insufficient evidence to support routine calcium supplementation of all pregnant women. However, high-risk groups, such as pregnant teens, populations with inadequate calcium intake, and women at risk of developing PIH, may benefit from consuming additional dietary calcium. *Am J Clin Nutr* 2000;71(suppl):1371S–4S.

KEY WORDS Dietary calcium, calcium supplementation, pregnancy, blood pressure, pregnancy-induced hypertension, gestational hypertension, preeclampsia, eclampsia

INTRODUCTION

Pregnancy-induced hypertension (PIH), which occurs in ≈10% of pregnancies, is a major risk factor for maternal and perinatal morbidity and mortality (1). PIH includes gestational hypertension as well as preeclampsia and eclampsia. Gestational hypertension is characterized by an abnormal rise in blood pressure that usually develops after the 20th week of pregnancy. In addition to hypertension, symptoms of preeclampsia include proteinuria and edema. If the condition progresses to eclampsia, life-threatening convulsions and coma can occur. PIH can also result in preterm labor and delivery and low-birth-weight infants.

Results from epidemiologic studies and clinical trials of nonpregnant adults suggest that dietary calcium may play a role in the etiology, prevention, and treatment of primary hypertension [reviewed by Hamet (2)]. For example, in the Dietary Approaches to Stop Hypertension (DASH) trial, feeding a combination diet consisting of 8–10 servings/d of fruit and vegetables and nearly 3 servings/d of low-fat dairy products resulted in reductions in systolic and diastolic blood pressure of 5.5 and 3.0 mm Hg, respectively, compared with the control diet (low in fruit, vegetables, and dairy products), and reductions of 2.7 and 1.9 mm Hg, respectively, compared with a diet high in fruit and vegetables only (3). Although the nutrient or nutrients in dairy products responsible for the observed blood pressure–lowering effect could not be identified in the DASH study, calcium is a likely contributor. A recent meta-analysis of 33 randomized, controlled clinical trials involving a total of 2412 patients showed that daily supplementation with 1000–2000 mg Ca reduced systolic blood pressure by 1.27 mm Hg (95% CI: −2.25, −0.29) (4). The more modest reduction in diastolic blood pressure of 0.24 mm Hg (95% CI: −0.92, 0.44) was not significant. Although the effect of calcium on blood pressure in the general population appears modest, calcium supplementation may be more relevant for certain subgroups, such as sodium-sensitive individuals, populations with inadequate calcium intake, and women with PIH (2, 4).

CALCIUM METABOLISM DURING PREGNANCY

To provide the calcium necessary for fetal bone mineralization, the maternal demand for calcium during pregnancy is elevated by as much as 300 mg/d (5). The normal expansion of maternal blood volume and the pregnancy-induced increase in urinary calcium excretion (6) that occur in well-nourished women add further to the physiologic calcium requirement. This additional calcium is normally provided by an increase in maternal intestinal calcium absorption (6). An increase in dietary calcium intake may not be necessary. Recently, the Food and Nutrition Board of the Institute of Medicine set the dietary reference intake for calcium at 1000 mg/d for women aged 19–50 y, and at 1300 mg/d for women ≤18 y, irrespective of pregnancy (7).

The precise factors involved in the pathogenesis of PIH are unclear, but several associated alterations in calcium metabolism have been identified. Possible metabolic abnormalities include a decrease in serum 1,25-dihydroxyvitamin D concentration (8), a decrease in serum ionized calcium concentration (9), and a decrease in urinary calcium excretion (10). Whether these biochemical abnormalities are a consequence of PIH or result from impaired calcium absorption, inadequate dietary calcium intake, or both is unclear. Calcium absorption has not been measured in

[1] From the Department of Nutritional Sciences, University of California, Berkeley, and the US Department of Agriculture Agricultural Research Service Western Human Nutrition Research Center, University of California, Davis.

[2] Presented at the symposium Maternal Nutrition: New Developments and Implications, held in Paris, June 11–12, 1998.

[3] Address reprint requests to LD Ritchie, the Department of Nutritional Sciences, University of California, Berkeley, CA 94720-3104.

hypertensive pregnant women. Epidemiologic data suggest, however, an inverse correlation between dietary calcium intake and incidence of PIH in diverse populations (11, 12). For example, in rural Guatemala, despite the low socioeconomic status and low intake of protein and energy of women, the incidence of eclampsia is low (≈0.4 per 1000 births) (11). Dietary calcium in this population is relatively high (≈1100 mg/d), in large part because of the incorporation of lime-processed tortillas as a staple component of the diet. Alternatively, in Colombia and India, where calcium intakes range from 250 to 350 mg/d, the incidence of eclampsia is higher (1.6 and 12.0 per 1000 births, respectively) (11). In a study by Marcoux et al (12) of women with a relatively high intake of dietary calcium, an association between the incidence of gestational hypertension and dietary calcium intake was observed. For gestational hypertension there was a continuous decrease in the adjusted odds ratio from 1 to 0.60 for the lowest (median: 764 mg/d for control subjects) to the highest (median: 2330 mg/d for control subjects) tertiles of calcium intake (12). Interestingly, no such association was observed for women with preeclampsia. The researchers hypothesized that women with gestational hypertension are a heterogeneous group; some women may experience a less severe form of preeclampsia whereas other women may have primary hypertension first revealed during pregnancy (12). Women with primary hypertension that is exposed during pregnancy may be most responsive to dietary calcium.

Another biochemical abnormality observed in some hypertensive pregnant women is an elevated concentration of intracellular free calcium. For example, compared with normotensive control subjects, women with preeclampsia have elevated intracellular calcium concentrations in erythrocytes (13) and platelets (14). Not all studies, however, found significant differences in the intracellular calcium concentration between hypertensive and normotensive women (15, 16). In the prospective study by Zemel et al (16), although no significant difference in basal platelet intracellular calcium concentration was found, preeclamptic patients had significantly greater intracellular calcium concentrations in platelets in response to stimulation by arginine vasopressin than did normotensive women. Differences in timing of blood measurements, biochemical methods used, experimental design, and dietary intakes of subjects may have contributed to contrasting study results. If established, however, an increase in intracellular calcium in vascular smooth muscle cells during pregnancy is consistent with development of vasoconstriction and resultant hypertension. Analogously, an increase in intracellular calcium in uterine smooth muscle cells is consistent with induction of preterm labor. Alternatively, it has been hypothesized that calcium affects smooth muscle cell contractility indirectly by influencing the production of other vasoactive agents such as nitric oxide, prostacyclins, or angiotensin (via the renin-angiotensin-aldosterone metabolic pathway) (11, 17).

The biochemical mechanism responsible for the possible increase in intracellular calcium and concomitant decrease in extracellular calcium is presently unclear. It has been suggested that parathyroid hormone plays a crucial role in influencing cation transport (17). Unfortunately, studies of parathyroid hormone concentrations during uncomplicated and hypertensive pregnancies have been inconclusive, undoubtedly complicated by differences in study design, assay methods, and dietary intakes. For example, normotensive pregnant women were reported to have higher (18), lower (19), or the same (6) serum parathyroid hormone concentrations as nonpregnant women. Similarly, women with PIH were found to have both lower (9) or the same (13) serum parathyroid hormone concentrations as normotensive, pregnant control subjects. Presently, the mechanisms responsible for any beneficial effect of calcium supplementation on blood pressure remain to be elucidated.

CALCIUM SUPPLEMENTATION DURING PREGNANCY

Numerous clinical trials of pregnant women have been conducted to assess the effects of calcium supplementation on PIH and pregnancy outcome. A meta-analysis by Bucher et al (20) was based on data from 2549 women in 14 randomized, controlled trials (considered the most scientifically sound of a total of 666 reviewed articles published between 1966 and 1994). Calcium supplementation in the range of 375–2000 mg (most studies closer to the upper boundary) resulted in a significant reduction in systolic blood pressure of 5.40 mm Hg (95% CI: −7.81, −3.00 mm Hg) and in diastolic blood pressure of 3.44 mm Hg (95% CI: −5.20, −1.68 mm Hg). Compared with placebo, calcium supplementation reduced the odds ratio for the development of gestational hypertension to 0.30 (95% CI: 0.17, 0.54) and of preeclampsia to 0.38 (95% CI: 0.22, 0.65). The findings were similar to those obtained in a previous meta-analysis of older clinical trials (21). Although some of the studies included in the more recent meta-analysis involved women at risk of developing PIH, most studies included only pregnant women who were initially normotensive (20). Thus it is possible that the blood pressure–lowering effect of calcium supplementation could be even greater in women with PIH. In support of this hypothesis, Knight and Keith (22), in a randomized, controlled clinical trial involving both normotensive and hypertensive pregnant women, reported that calcium supplementation (1000 mg/d) significantly lowered the diastolic blood pressure in the hypertensive group only.

Bucher et al (20) did not assess whether the effect of calcium supplementation on blood pressure and incidence of PIH was greater in women with habitually low dietary calcium intakes. In almost all cases in which diet information was provided, calcium intakes were less than the 1100 or 1300 mg/d dietary reference intake for pregnant women. Several of the studies included in the meta-analysis were performed in the Andes of rural Ecuador, where typical calcium intakes during pregnancy were ≈300 mg/d (23–25). Also included in the study were women from Guatemala (26), Argentina (27), and India (28), where intakes averaged ≈600–800 mg/d, 650 mg/d, and 500 mg/d, respectively. Several studies included mostly African Americans (22, 29) or women with low socioeconomic status (30); calcium intakes, when provided, were in the range of 600–650 mg/d. In only 2 studies was the average calcium intake of the women near or at the dietary reference intake: in the range of 900–1100 mg/d in a group including African Americans and white Argentinians (31) and ≈1200 mg/d in a group of teenagers (32).

Conflicting with the most recent meta-analysis (20) are results from the newly published multicenter Calcium for Preeclampsia Prevention (CPEP) trial conducted in the United States by Levine et al (33). The CPEP trial, which included 4589 women of various ethnic and socioeconomic backgrounds whose average calcium intake was ≈1100 mg/d, found no significant effect of supplementation with 2000 mg Ca daily on blood pressure or incidence of preeclampsia or PIH. One obvious explanation for the discrepancy between this clinical trial and the meta-analysis

by Bucher et al (20) is that supplemental calcium may exert an effect only in women whose diets are inadequate in calcium. However, in the CPEP trial no benefit was observed even among the women (n = 884) whose calcium intakes were in the lowest quintile (median intake of 422 mg/d).

An alternative explanation for the discrepancy between the meta-analysis by Bucher et al (20) and the clinical trial by Levine et al (33) involves the age of the study subjects. Several studies (23, 24, 30, 32) in the meta-analysis included a large proportion of pregnant teens, whose demand for calcium exceeds that of a pregnant adult because of continued maternal bone mineralization (34). In support of this hypothesis are results from a recent randomized, controlled clinical trial in Ecuador of 260 teens (<17.5 y of age; average dietary calcium intake: ≈600 mg/d) supplemented with 2000 mg Ca/d or placebo (35). Calcium supplementation resulted in a significant decrease in systolic and diastolic blood pressures (9.1 and 6.0 mm Hg, respectively) and a significant 12.4% decline in the risk of preeclampsia. However, even among the youngest women in the CPEP trial (aged 12–16 y; n = 665), calcium supplementation did not provide any detectable beneficial effect (33).

EFFECTS OF MATERNAL CALCIUM SUPPLEMENTATION ON OFFSPRING

The meta-analysis by Bucher et al (20) also examined the effect of calcium supplementation on pregnancy outcome. Compared with placebo, calcium supplementation did not significantly reduce the incidence of preterm delivery (odds ratio: 0.69; 95% CI: 0.48, 1.01). Similarly, although a trend existed in favor of calcium supplementation in reducing cesarean delivery, intrauterine growth retardation, and intrauterine or perinatal death, in every case the upper boundary of the CI included a small detrimental effect. One possible explanation for finding a significant blood pressure–lowering effect, without a concomitant effect on pregnancy outcome, is that fewer studies of pregnancy outcome (eg, n = 5 for preterm delivery) were available. However, the CPEP trial also found no significant effect of calcium supplementation on the number of infants delivered preterm, small-for-gestational age births, or fetal and neonatal deaths (33). It remains possible that calcium supplementation may reduce the risk of hypertension and proteinuria without affecting conditions in the uterus (20).

It was recently suggested that maternal diet during fetal development may have a long-term effect on the blood pressure of offspring (36, 37). To examine this possibility Belizan et al (38) conducted a follow-up study of 591 children whose mothers had participated in a clinical trial of calcium supplementation during their pregnancy ≈7 y earlier. A trend toward a lower systolic blood pressure (mean difference: −1.4 mm Hg; 95% CI: −3.2, 0.5) was found in children whose mothers had been supplemented with calcium during pregnancy, compared with children whose mothers received placebo. The risk of high systolic blood pressure was significantly lower in the calcium group than in the placebo group (relative risk: 0.59; 95% CI: 0.39, 0.90).

CONCLUSION

Evidence suggests a possible beneficial effect of dietary calcium in the prevention and treatment of PIH. However, contradictions persist in calcium intervention studies of pregnant women. A definitive understanding of the mechanism whereby dietary calcium influences blood pressure is also lacking. At present, there is not enough evidence to support routine calcium supplementation of all pregnant women. However, high-risk groups, such as pregnant teens, populations with inadequate calcium intake, and women at risk of developing PIH, may benefit from consuming additional dietary calcium. Future research is necessary to identify women who stand to benefit most from increasing their calcium intake. It may also be of interest to determine whether women with PIH have impaired calcium absorption, whether the timing of calcium supplementation is important [eg, early in pregnancy when alterations in calcium homeostasis are already beginning to occur (6) as opposed to in mid pregnancy when most clinical trials begin supplementation], and whether consumption of dairy foods has a larger impact than does supplemental calcium alone.

REFERENCES

1. Hypertensive disorders in pregnancy. In: Cunningham FG, MacDonald PC, Gant NF, eds. Williams obstetrics. 18th ed. Norwalk, CT: Appleton & Lange, 1989:653–94.
2. Hamet P. The evaluation of the scientific evidence for a relationship between calcium and hypertension. J Nutr 1995;125:311S–400S (Life Sciences Research Office Report).
3. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med 1997; 336:1117–24.
4. Bucher HC, Cook RJ, Guyatt GH, et al. Effects of dietary calcium supplementation on blood pressure: a meta-analysis of randomized controlled trials. JAMA 1996;275:1016–22.
5. Reeve J. Calcium metabolism. In: Hytten F, Chamberlain G, eds. Clinical physiology in obstetrics. Oxford, United Kingdom: Blackwell Scientific Publications, 1980:257–69.
6. Ritchie LD, Fung EB, Halloran BP, et al. A longitudinal study of calcium homeostasis during human pregnancy and lactation and after resumption of menses. Am J Clin Nutr 1998;67:693–701.
7. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. Dietary reference intakes (DRIs) for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press, 1997.
8. Frolich A, Rudnicki M, Storm T, Rasmussen N, Hegedus L. Impaired 1,25-dihydroxyvitamin D production in pregnancy-induced hypertension. Eur J Obstet Gynecol Reprod Biol 1992;47:25–9.
9. Varner MW, Cruikshank DP, Pitkin RM. Calcium metabolism in the hypertensive mother, fetus and newborn infant. Am J Obstet Gynecol 1983;147:762–5.
10. Taufield PA, Ales KL, Resnick LM, Druzin ML, Gertner JM, Laragh JH. Hypocalciuria in preeclampsia. N Engl J Med 1987;316:715–8.
11. Repke JT, Villar J. Pregnancy-induced hypertension and low birth weight: the role of calcium. Am J Clin Nutr 1991;54(suppl): 237S–41S.
12. Marcoux S, Brisson J, Fabia J. Calcium intake from dairy products and supplements and the risks of preeclampsia and gestational hypertension. Am J Epidemiol 1991;133:1266–72.
13. Sowers JR, Zemel MB, Bronsteen RA, et al. Erythrocyte cation metabolism in preeclampsia. Am J Obstet Gynecol 1989;161:441–5.
14. Haller H, Oeney T, Hauck U, Distler A, Philipp T. Increased intracellular free calcium and sensitivity to angiotensin II in platelets of preeclamptic women. Am J Hypertens 1989;2:238–43.
15. Barr SM, Lees KR, Butters L, O'Donnell A, Rubin PC. Platelet intracellular free calcium concentration in normotensive and hypertensive pregnancies in the human. Clin Sci 1989;76:67–71.
16. Zemel MB, Zemel PC, Berry S, et al. Altered platelet calcium metabolism as an early predictor of increased peripheral vascular

resistance and preeclampsia in urban black women. N Engl J Med 1990;323:434–8.
17. Myatt L. The relation of calcium nutrition and metabolism to preeclampsia and premature labor. In: Tsang RC, Mimouni F, eds. Calcium nutriture for mothers and children. New York: Raven Press, 1992:129–41.
18. Okonofua F, Menon RK, Houlder S, et al. Calcium, vitamin D and parathyroid hormone relationships in pregnant Caucasian and Asian women and their neonates. Ann Clin Biochem 1987;24:22–8.
19. Frolich A, Rudnicki M, Fischer-Rasmussen W, Olofsson K. Serum concentrations of intact parathyroid hormone during late human pregnancy: a longitudinal study. Eur J Obstet Gynecol Reprod Biol 1991;42:85–7.
20. Bucher HC, Guyatt GH, Cook RJ, et al. Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia: a meta-analysis of randomized controlled trials. JAMA 1996;275: 1113–7.
21. Carroli G, Duley L, Belizan JM, Villar J. Calcium supplementation during pregnancy: a systematic review of randomized controlled trials. Br J Obstet Gynaecol 1994;101:753–8.
22. Knight KB, Keith RE. Calcium supplementation on normotensive and hypertensive pregnant women. Am J Clin Nutr 1992;55: 891–5.
23. Lopez-Jaramillo P, Narvaez M, Weigel RM, Yepez R. Calcium supplementation reduces the risk of pregnancy-induced hypertension in an Andes population. Br J Obstet Gynaecol 1989;96:648–55.
24. Lopez-Jaramillo P, Narvaez M, Felix C, Lopez A. Dietary calcium supplementation and prevention of pregnancy hypertension. Lancet 1990;335:293 (letter).
25. Felix C, Jacome P, Lopez A, Moya W, Narvaez M, Lopez-Jaramillo P. The hypotensive effect of calcium supplementation during normal pregnancy in Andean women is not related to vascular production of prostacyclin by umbilical arteries. J Obstet Gynaecol 1991; 11:93–6.
26. Belizan JM, Villar J, Zalazar A, Rojas L, Chan D, Bryce GF. Preliminary evidence of the effect of calcium supplementation on blood pressure in normal pregnant women. Am J Obstet Gynecol 1983;146:175–80.
27. Belizan JM, Villar J, Gonzalez L, Campodonico L, Bergel E. Calcium supplementation to prevent hypertensive disorders of pregnancy. N Engl J Med 1991;325:1399–405.
28. Marya RK, Rathee S, Manrow M. Effect of calcium and vitamin D supplementation on toxaemia of pregnancy. Gynecol Obstet Invest 1987;24:38–42.
29. Repke JT, Villar J, Anderson C, Pareja G, Dubin N, Belizan JM. Biochemical changes associated with blood pressure reduction induced by calcium supplementation during pregnancy. Am J Obstet Gynecol 1989;160:684–90.
30. Sanchez-Ramos L, Briones DK, Kaunitz AM, Delvalle GO, Gaudier FL, Walker CD. Prevention of pregnancy-induced hypertension by calcium supplementation in angiotensin II-sensitive patients. Obstet Gynecol 1994;84:349–53.
31. Villar J, Repke J, Belizan JM, Pareja G. Calcium supplementation reduces blood pressure during pregnancy: results of a randomized controlled clinical trial. Obstet Gynecol 1987;70:317–22.
32. Villar J, Repke JT. Calcium supplementation during pregnancy may reduce preterm delivery in high-risk populations. Am J Obstet Gynecol 1990;163:1124–31.
33. Levine RJ, Hauth JC, Curet LB, et al. Trial of calcium to prevent preeclampsia. N Engl J Med 1997;337:69–76.
34. Matkovic V, Jelic T, Wardlaw GM, et al. Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. Inference from a cross-sectional model. J Clin Invest 1994;93:799–808.
35. Lopez-Jaramillo P, Delgado F, Jacome P, Teran E, Ruano C, Rivera J. Calcium supplementation and the risk of preeclampsia in Ecuadorian pregnant teenagers. Obstet Gynecol 1997;90:162–7.
36. Godfrey KM, Forrester T, Barker DJ, et al. Maternal nutritional status in pregnancy and blood pressure in childhood. Br J Obstet Gynaecol 1994;101:398–403.
37. Campbell DM, Hall MH, Barker DJ, Cross J, Shiell AW, Godfrey KM. Diet in pregnancy and the offspring's blood pressure 40 years later. Br J Obstet Gynaecol 1996;103:273–80.
38. Belizan JM, Villar J, Bergel E, et al. Long term effect of calcium supplementation during pregnancy on the blood pressure of offspring: follow up of a randomized controlled trial. BMJ 1997;315:281–5.

The American Journal of Clinical Nutrition