

The New England Journal of Medicine

© Copyright, 1997, by the Massachusetts Medical Society

VOLUME 337

JULY 10, 1997

NUMBER 2



TRIAL OF CALCIUM TO PREVENT PREECLAMPSIA

RICHARD J. LEVINE, M.D., JOHN C. HAUTH, M.D., LUIS B. CURET, M.D., BAHA M. SIBAI, M.D.,
PATRICK M. CATALANO, M.D., CYNTHIA D. MORRIS, PH.D., REBECCA DERSIMONIAN, Sc.D., JOY R. ESTERLITZ, M.S.,
ELIZABETH G. RAYMOND, M.D., DIANE E. BILD, M.D., JOHN D. CLEMENS, M.D., AND JEFFREY A. CUTLER, M.D.

ABSTRACT

Background Previous trials have suggested that calcium supplementation during pregnancy may reduce the risk of preeclampsia. However, differences in study design and a low dietary calcium intake in the populations studied limit acceptance of the data.

Methods We randomly assigned 4589 healthy nulliparous women who were 13 to 21 weeks pregnant to receive daily treatment with either 2 g of elemental calcium or placebo for the remainder of their pregnancies. Surveillance for preeclampsia was conducted by personnel unaware of treatment-group assignments, using standardized measurements of blood pressure and urinary protein excretion at uniformly scheduled prenatal visits, protocols for monitoring these measurements during the hospitalization for delivery, and reviews of medical records of unscheduled outpatient visits and all hospitalizations.

Results Calcium supplementation did not significantly reduce the incidence or severity of preeclampsia or delay its onset. Preeclampsia occurred in 158 of the 2295 women in the calcium group (6.9 percent) and 168 of the 2294 women in the placebo group (7.3 percent) (relative risk, 0.94; 95 percent confidence interval, 0.76 to 1.16). There were no significant differences between the two groups in the prevalence of pregnancy-associated hypertension without preeclampsia (15.3 percent vs. 17.3 percent) or of all hypertensive disorders (22.2 percent vs. 24.6 percent). The mean systolic and diastolic blood pressures during pregnancy were similar in both groups. Calcium did not reduce the numbers of preterm deliveries, small-for-gestational-age births, or fetal and neonatal deaths; nor did it increase urolithiasis during pregnancy.

Conclusions Calcium supplementation during pregnancy did not prevent preeclampsia, pregnancy-associated hypertension, or adverse perinatal outcomes in healthy nulliparous women. (N Engl J Med 1997; 337:69-76.)

©1997, Massachusetts Medical Society.

ABOUT 5 percent of all pregnant women have preeclampsia, defined as hypertension and proteinuria beginning during the second half of gestation.¹ Preeclampsia is a leading cause of maternal death throughout the world and is accompanied by substantial perinatal morbidity and mortality.² The search for an effective preventive therapy has therefore been a major focus of obstetrical investigation.

The results of 13 clinical trials³⁻¹⁵ and several meta-analyses¹⁶⁻²⁰ have suggested that calcium supplementation reduces the incidence of preeclampsia. Critical review of these reports, however, reveals important differences in study design that limit acceptance of these past trials.^{17,19,21,22} Many were conducted in countries where, unlike the United States, the usual diet contains little calcium.^{3-5,7-9,11,14} In response to the need for a more definitive evaluation of calci-

From the Division of Epidemiology, Statistics, and Prevention Research, National Institute of Child Health and Human Development, Bethesda, Md. (R.J.L., R.D., E.G.R., J.D.C.); the Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham (J.C.H.); the Department of Obstetrics and Gynecology, University of New Mexico Health Sciences Center, Albuquerque (L.B.C.); the Department of Obstetrics and Gynecology, University of Tennessee College of Medicine, Memphis (B.M.S.); the Department of Obstetrics and Gynecology, MetroHealth Medical Center, Case Western Reserve University, Cleveland (P.M.C.); the Department of Medicine, Oregon Health Sciences University, Portland (C.D.M.); the Emmes Corporation, Potomac, Md. (J.R.E.); Family Health International, Research Triangle Park, N.C. (E.G.R.); and the Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, Md. (D.E.B., J.A.C.). Address reprint requests to Dr. Levine at the Division of Epidemiology, Statistics, and Prevention Research, National Institute of Child Health and Human Development, National Institutes of Health, Bldg. 6100, Rm. 7B03, Bethesda, MD 20892-7510.

Other authors were Marian G. Ewell, Sc.D. (Emmes Corp., Potomac, Md.), Steven A. Friedman, M.D. (University of Tennessee College of Medicine, Memphis), Robert L. Goldenberg, M.D. (University of Alabama at Birmingham), Sig-Linda Jacobson, M.D. (Oregon Health Sciences University, Portland), Gary M. Joffe, M.D. (University of New Mexico Health Sciences Center, Albuquerque), Mark A. Klebanoff, M.D. (National Institute of Child Health and Human Development, Bethesda, Md.), and Alice S. Petrusis, M.D. (MetroHealth Medical Center, Cleveland).

um supplementation to prevent preeclampsia in the United States, the Calcium for Preeclampsia Prevention (CPEP) trial was undertaken at five U.S. medical centers.

METHODS

Subjects

The study protocol was approved by the institutional review boards at the five participating medical centers, and all the women gave written informed consent.

We assembled the potential study cohort by screening nulliparous women who were 11 to 21 weeks pregnant to exclude those who were taking medications or had obstetrical conditions, pre-existing diseases, or personal characteristics that could markedly influence the study end points, the absorption or metabolism of calcium, any risk associated with calcium supplementation, or compliance. To minimize the possibility of urolithiasis, we excluded women with elevated serum concentrations of creatinine (≥ 1.0 mg per deciliter [$88.4 \mu\text{mol}$ per liter]) or calcium (≥ 10.6 mg per deciliter [2.6 mmol per liter]), those with renal disease, hematuria, or a history of urolithiasis in themselves or a first-degree relative, and those who reported frequent use of calcium supplements or antacids. The eligible women then underwent a single-blind test of compliance with medication, during which they were asked to take two placebo tablets with their morning and evening meals for 6 to 14 days. Women were enrolled in the trial if they took at least 75 percent of the placebo tablets during the test, if both before and after the test their blood pressure was 134/84 mm Hg or less and a dipstick test for urinary protein was negative or showed only a trace, and if they were 13 to 21 weeks pregnant as determined by ultrasonography or by menstrual dates confirmed by ultrasonography. A detailed description of the screening and selection procedures, including a complete list of exclusion criteria, has been published previously.²¹

Of 11,959 nulliparous women screened, 5703 were excluded before the compliance test. Only about one fifth of the exclusions were for medical reasons, most often a personal or family history of urolithiasis. An additional 1667 women were excluded after the compliance test. The remaining 4589 women were enrolled in the double-blind study of calcium supplementation or placebo. Women began treatment on the day of enrollment, which was before the 22nd week of gestation.

Additional Base-Line Evaluations

To determine whether calcium supplementation would be more beneficial to women with lower dietary calcium intake or urinary calcium excretion at base line, dietary intake was estimated by means of a 24-hour dietary-recall report obtained by a specially trained dietician or research nurse and 24-hour and first morning urine specimens were collected for calcium and creatinine measurements.

Medications

The chewable study tablets, consisting largely of cornstarch and confectioner's sugar, were packaged individually in blister packs. The calcium tablets also contained 500 mg of elemental calcium as calcium carbonate. Fifty tablets each of calcium and placebo were selected at random for analysis. The mean calcium content of the calcium tablets was 485 mg (range, 453 to 539). None of the placebo tablets contained calcium (< 30 mg). The women were instructed to take two tablets with each of their morning and evening meals until delivery, diagnosis of preeclampsia, or suspicion of urolithiasis. They were also asked to drink at least six glasses of fluid per day.

In addition, the women were given a daily prenatal supplement (Mission Prenatal) containing 50 mg of elemental calcium, 30 mg of iron, 400 units of vitamin D₂, and other vitamins.²¹ Acetaminophen tablets (Tylenol) and an antacid not containing cal-

cium (Mylanta) were dispensed as needed, but the women were asked not to take other supplements, analgesics, or antacids.

Randomization

Packages of study tablets were prepared and numbered by the pharmaceutical manufacturer according to a computer-generated simple randomization sequence developed by the study statisticians. The packages were then shipped to the medical centers. On enrollment, each woman was assigned the next numbered package of medication at that center.

Surveillance for Hypertension and Proteinuria

We conducted surveillance for hypertension and proteinuria using standardized measurements of blood pressure and urinary protein excretion at uniformly scheduled clinic visits, protocols for monitoring these measurements during the hospitalization for delivery, and reviews of the medical records of unscheduled outpatient visits and all hospitalizations until 24 hours post partum.

The women were to be examined by trained staff members every 4 weeks through the 29th week of gestation, every 2 weeks through the 35th week, and weekly thereafter. Blood pressure was measured with the subject in the sitting position by a certified examiner using a standard mercury sphygmomanometer according to a published protocol²¹; two measurements were taken at least one minute apart, and the results were averaged. Diastolic blood pressure was determined by using the fifth Korotkoff sound unless a measurement was zero, in which case the fourth sound was used. Voided urine was collected for the measurement of protein by dipstick. Proteinuria of $\geq 1+$ (300 mg per liter) was confirmed by testing a clean-catch, midstream sample.

Surveillance for Urolithiasis

At each clinic visit, a dipstick test for hematuria was performed and the women were asked about flank and groin pain and symptoms of urinary tract infection. If urolithiasis was suspected or hematuria confirmed (except if caused by a urinary tract infection that responded to therapy), renal ultrasonography was performed.²¹

Assessment of Compliance

The women were asked to return all the dispensed blister packs at every study visit and at the time of hospitalization for delivery. Compliance was computed by dividing the number of tablets removed from the returned blister packs by the total number of prescribed tablets.

Definitions of Outcomes

Pregnancy-associated hypertension was defined as a diastolic blood pressure of 90 mm Hg or greater on two occasions 4 to 168 hours (one week) apart. Severe pregnancy-associated hypertension was defined as a diastolic blood pressure of 110 mm Hg or greater on two occasions 4 to 168 hours apart, or on one occasion if the woman had received antihypertensive therapy. Severe pregnancy-associated hypertension was also diagnosed when pregnancy-associated hypertension was complicated by otherwise unexplained oliguria (< 400 ml of urine per 24 hours), pulmonary edema, or thrombocytopenia (two platelet counts $< 100,000$ per cubic millimeter).

Pregnancy-associated proteinuria was defined as any of the following: ≥ 300 mg of protein in a 24-hour urine sample, two urine specimens obtained 4 to 168 hours apart containing $\geq 1+$ protein as measured by dipstick, or a single urine specimen with a ratio of protein to creatinine (both measured in milligrams) of ≥ 0.35 or containing $\geq 2+$ protein as measured by dipstick. Catheterized specimens were required after membrane rupture or in the presence of vaginitis. Severe pregnancy-associated proteinuria was diagnosed if a 24-hour urine sample contained ≥ 3.5 g protein or if two urine specimens obtained 4 to 168 hours apart contained $\geq 3+$ protein (3000 mg per liter) as measured by dipstick. All other pregnancy-associated proteinuria was termed mild.

Preeclampsia was defined as pregnancy-associated hypertension and pregnancy-associated proteinuria occurring within seven days of each other. This period was selected to avoid the diagnosis of preeclampsia in women with hypertension at term but proteinuria (often from urinary tract infections) at a time remote from term. Eclampsia was diagnosed when a woman with pregnancy-associated hypertension had a seizure without any other known cause. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet counts) was defined as the presence of pregnancy-associated hypertension with two or more platelet counts of less than 100,000 per cubic millimeter, a serum aspartate aminotransferase concentration ≥ 70 U per liter, and a serum lactate dehydrogenase concentration ≥ 600 U per liter, a serum total bilirubin concentration ≥ 1.2 mg per deciliter (20.5 μ mol per liter), or a peripheral-blood smear with nucleated red cells or schistocytes. Severe preeclampsia was defined as preeclampsia with either severe pregnancy-associated hypertension or severe pregnancy-associated proteinuria, or as eclampsia or the HELLP syndrome with or without proteinuria.

Infants small for gestational age were defined as those whose birth weights were below the 10th percentile according to the standards of Brenner et al.²³ Neonatal hypocalcemia was defined as serum total calcium of less than 8.0 mg per deciliter (2.0 mmol per liter), or less than 7.0 mg per deciliter (1.7 mmol per liter) for infants of less than 37 weeks' gestation.

Urolithiasis was confirmed if a stone was recovered or seen on renal ultrasonography, radiography, computed tomography, or magnetic resonance imaging. Urolithiasis was suspected if the woman had hematuria and severe flank pain in the absence of pyuria, fever, and leukocytosis.

Nested Case-Control Studies of Urinary Calcium Excretion

Urinary calcium was measured by flame atomic absorption spectrophotometry.²⁴ Urinary creatinine was measured in a modified kinetic Jaffé reaction.^{25,26}

To determine whether calcium supplementation provided a greater benefit to women with lower urinary calcium excretion, nested case-control studies of base-line urinary calcium excretion were conducted in women with adequate first morning and 24-hour urine specimens. For each woman with preeclampsia, four women without hypertensive or proteinuric end points were randomly selected, matched for clinical center and the presence of a 24-hour urine sample that appeared to be adequate; an adequate sample was defined initially as one that had no visible blood and, for 24-hour specimens, no reported missing voids and a volume of at least 400 ml. Creatinine was then measured in the urine sample; if the value was 15 mg (132 μ mol) or more per kilogram of body weight, the sample was confirmed as being adequate.

Statistical Analysis

All the women randomly assigned to treatment were included in the primary analysis regardless of their follow-up status or compliance with treatment. Comparisons between the calcium and placebo groups for outcomes with discrete categories were performed by using a two-sided Mantel-Haenszel or Fisher's exact test at the 0.05 level. Risk ratios and 95 percent confidence intervals were estimated by the Mantel-Haenszel procedure.²⁷

Differences in blood pressure between the groups during weeks 20 to 40 of gestation were evaluated by a repeated-measures analysis after adjustment for base-line differences and the correlation of observations of the same woman.²⁸ Differences in the length of time until the onset of preeclampsia were assessed by life-table methods and the log-rank test.²⁹

RESULTS

Of 4589 women enrolled in the trial, 2295 were assigned to receive calcium and 2294 to receive placebo. The demographic and clinical characteristics

of the women in the two groups were similar (Table 1). Two hundred fifty-three women (5.5 percent) were lost to follow-up: 132 in the calcium group and 121 in the placebo group.

Compliance

The numbers of completed and missed study visits, unscheduled outpatient visits, and hospitalizations were similar in the two groups. Compliance with medication averaged 64 percent in the calcium group and 67 percent in the placebo group ($P < 0.001$). The median daily consumption of calcium from all sources in the calcium group (base-line dietary intake plus supplemental calcium actually taken) was more than twice that in the placebo group (2369 vs. 982 mg).

Incidence of Hypertensive Disorders and Proteinuria

The frequency of hypertensive disorders and proteinuria in each treatment group is shown in Table 2. The incidence of preeclampsia was 6.9 percent in the calcium group and 7.3 percent in the placebo group (relative risk, 0.94; 95 percent confidence interval, 0.76 to 1.16). There were no statistically sig-

TABLE 1. CHARACTERISTICS OF THE NULLIPAROUS PREGNANT WOMEN AT ENROLLMENT, ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	CALCIUM GROUP (N=2295)	PLACEBO GROUP (N=2294)
Age (yr)	21±4	21±4
Height (cm)	162±7	162±7
Weight (kg)	68±17	68±17
Body-mass index†	26±6	26±6
Upper-arm circumference (cm)	28±4	27±5
Blood pressure (mm Hg)		
Systolic	106.4±8.7	106.6±8.8
Diastolic	59.6±8.0	59.8±7.6
Week of gestation	17.2±2.5	17.1±2.5
Previous abortion (%)	25	25
Race (%)		
White non-Hispanic	35	35
White Hispanic	16	18
Black, including black Hispanic	46	44
Other or unknown‡	2	2
Current smoker (%)	12	12
Daily calcium intake (mg)§	1113±691	1135±675
Highest grade of school completed	12±2	12±2
Private health insurance (%)	11	10
Never married (%)	77	77
Medication taken during compliance test (% of tablets)	94	93¶

*Plus-minus values are means ±SD.

†Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡The races of six women in each treatment group were not known.

§The category includes calcium from prenatal vitamins and supplements.

¶ $P = 0.05$ for the comparison with the calcium group.

TABLE 2. INCIDENCE OF HYPERTENSIVE DISORDERS AND PROTEINURIA DURING PREGNANCY, ACCORDING TO TREATMENT GROUP.*

CONDITION	CALCIUM GROUP (N = 2295)	PLACEBO GROUP (N = 2294)	RELATIVE RISK (95% CI)†
	no. (%)		
Preeclampsia	158 (6.9)	168 (7.3)	0.94 (0.76–1.16)
Mild	108 (4.7)	109 (4.8)	0.99 (0.76–1.28)
Severe	50 (2.2)	59 (2.6)	0.85 (0.58–1.23)
Pregnancy-associated hypertension without preeclampsia‡	351 (15.3)	397 (17.3)	0.88 (0.78–1.01)
Mild	335 (14.6)	381 (16.6)	0.88 (0.77–1.01)
Severe	16 (0.7)	16 (0.7)	1.00 (0.50–1.99)
All hypertensive disorders	509 (22.2)	565 (24.6)	0.90 (0.81–1.00)
Pregnancy-associated proteinuria without pregnancy-associated hypertension	77 (3.4)	76 (3.3)	1.01 (0.74–1.38)

*The table includes all the women randomly assigned to a treatment group.

†The relative risks are those for a woman in the calcium group as compared with a woman in the placebo group. CI denotes confidence interval.

‡This category includes 9 and 10 women in the calcium and placebo groups, respectively, who had pregnancy-associated hypertension and pregnancy-associated proteinuria, but not preeclampsia, since the events did not occur within a week of each other.

nificant differences between the groups in the incidence of pregnancy-associated hypertension without preeclampsia, pregnancy-associated proteinuria without hypertension, or all hypertensive disorders. Moreover, significant differences between the treatment groups were not detected when preeclampsia and pregnancy-associated hypertension without preeclampsia were examined within categories of severity (Table 2), at individual medical centers, or among white Hispanic, white non-Hispanic, or black (including black Hispanic) women (data not shown). The HELLP syndrome and eclampsia were not less frequent in the calcium group; there were seven and four cases, respectively, as compared with two and four in the placebo group.

The relative risks of preeclampsia (Fig. 1) and of pregnancy-associated hypertension without preeclampsia (data not shown) did not differ according to the quintile of base-line dietary calcium intake, the level of compliance with medication, or the age stratum, and the results of tests for interaction between the treatment group and each of these risk factors were not significant. Similarly, stratified analyses did not indicate a greater benefit from calcium supplementation with shorter duration of gestation at enrollment. Odds ratios for the occurrence of preeclampsia in the treatment groups did not differ according to whether the woman's base-line 24-hour

urinary calcium excretion or ratio of urinary calcium to creatinine in the first morning urine was above or below the median (212 mg [5.3 mmol] or a ratio of 0.153 with measurements in milligrams [0.4327 with measurements in millimoles]) or above or below the median ratio of a previous study (0.22 with measurements in milligrams [0.62 with measurements in millimoles]).¹¹ There was no significant difference between treatment groups in duration of gestation at the onset of preeclampsia.

Blood pressures at scheduled clinic visits are shown according to the duration of gestation in Figure 2. The mean systolic blood pressure during weeks 20 to 40 of gestation was slightly, but not significantly, lower in the calcium group (by 0.3 mm Hg; 95 percent confidence interval, 0.7 mm Hg lower to 0.1 mm Hg higher). The diastolic pressure, however, was minimally higher in the calcium group (by 0.03 mm Hg; 95 percent confidence interval, 0.3 mm Hg lower to 0.4 mm Hg higher).

Obstetrical Complications and Perinatal Outcomes

There were no significant differences between the groups in important obstetrical complications (Table 3) or perinatal outcomes (Table 4). Neither urolithiasis during pregnancy nor neonatal hypocalcemia was significantly increased in the calcium group.

DISCUSSION

In this study, supplementation with 2 g of calcium daily did not reduce the incidence or severity of preeclampsia or delay its onset, nor did it reduce the incidence of pregnancy-associated hypertension without preeclampsia. When the analyses were stratified according to compliance, there was no effect on preeclampsia or on pregnancy-associated hypertension without preeclampsia, even among the women who were most compliant with treatment. Blood pressures during pregnancy were similar in the treatment groups, as was consistent with the absence of any effect on preeclampsia or pregnancy-associated hypertension.

Calcium supplementation might be expected to be of greater benefit to women with lower intakes of dietary calcium. In one trial, a low ratio of urinary calcium to creatinine in the first morning urine at the time of enrollment, which could reflect a low dietary intake, was a predictor of benefit.¹¹ However, we detected no benefit in women with low base-line 24-hour urinary calcium excretion or low ratios of urinary calcium to creatinine in the first morning urine. Nor was there any benefit among women whose base-line dietary calcium intakes were in the lowest quintile and whose median daily intake of 422 mg was similar to or less than that reported for women in many developing countries.^{7,8,11} The biologic demand for calcium during pregnancy is greatest during adolescence, when calcium is needed for

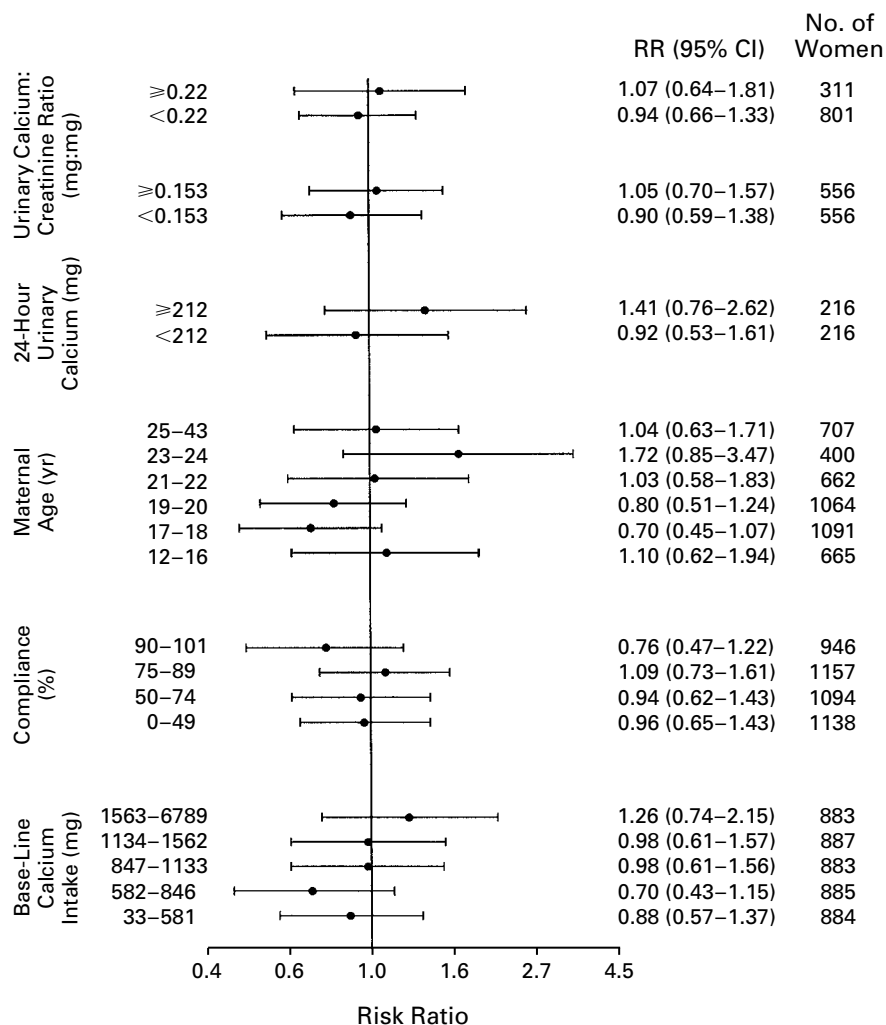


Figure 1. Effect of Calcium Supplementation on the Incidence of Preeclampsia.

Shown are the risk ratios (RR) for preeclampsia, 95 percent confidence intervals (CI), and numbers of women according to the base-line ratio of calcium to creatinine in a first morning urine sample, the base-line 24-hour urinary calcium excretion, maternal age, the percent compliance with the study treatment, and the base-line dietary calcium intake. Risk ratios are adjusted for medical center and are relative risks, except for those for the base-line 24-hour urinary calcium excretion and the base-line ratio of calcium to creatinine in a first morning urine sample, which are odds ratios. Values less than 1.0 indicate a protective effect. Urinary calcium excretion of 212 mg is equivalent to 5.3 mmol, and urinary ratios of calcium to creatinine of 0.22 and 0.153 with measurements in milligrams are equivalent to 0.62 and 0.4327, respectively, with measurements in millimoles.

both maternal and fetal growth. The youngest women, therefore, might be expected to derive the greatest benefit from calcium supplementation. Nevertheless, we found no benefit in 12-to-16-year-olds.

It has been suggested that calcium supplementation might also reduce the incidence of preterm deliveries, cesarean deliveries, births of infants small for their gestational ages, and perinatal deaths.^{18,20} These beneficial consequences would be due in part to the prevention of preeclampsia and pregnancy-associated hypertension but could theoretically also

result from direct effects on uterine smooth muscle to reduce contractility and prevent preterm labor.¹⁰ We found no reduction in obstetrical complications or adverse perinatal outcomes among women assigned to receive calcium supplementation.

Urinary calcium excretion rises in normal pregnant women because of increased intestinal absorption.³⁰ The addition of 2 g of calcium to the diet, therefore, could further increase urinary calcium excretion and thus the risk of renal calculi.³¹ We did not find an increase in renal calculi among the women who re-

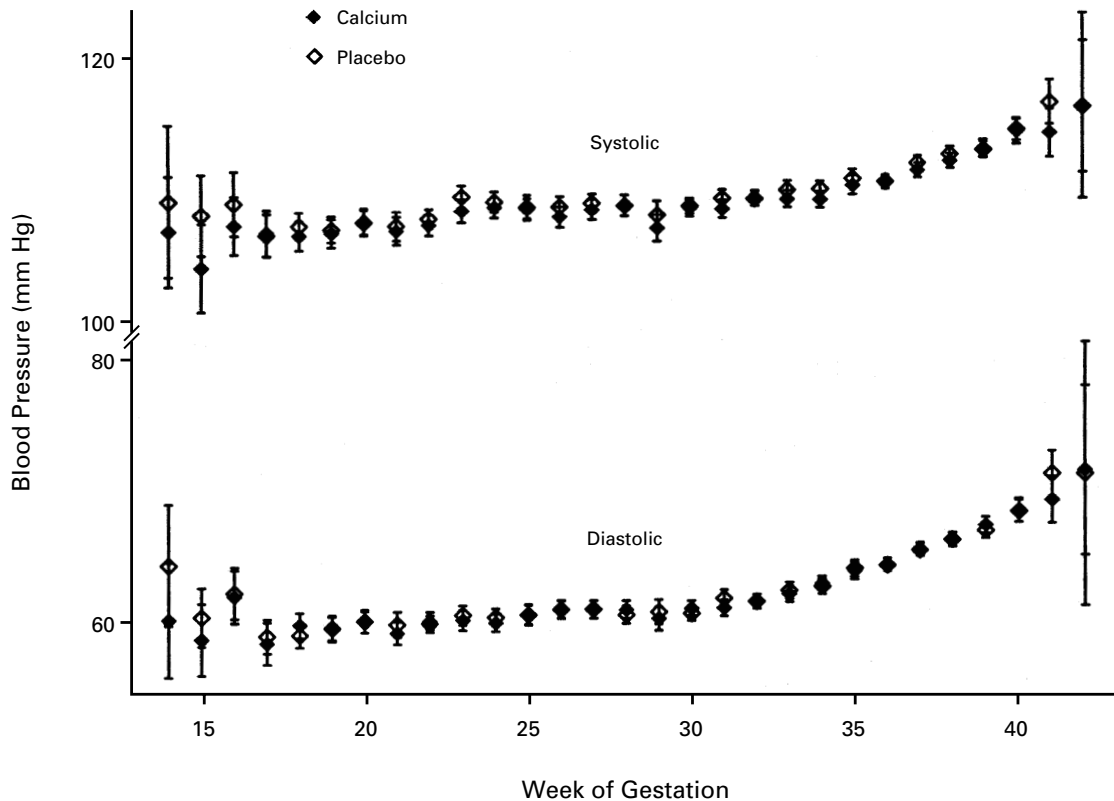


Figure 2. Mean (\pm SE) Diastolic and Systolic Blood Pressures at Scheduled Clinic Visits in the Calcium and Placebo Groups According to the Week of Gestation.

Measurements for one woman at 43 weeks were excluded, and measurements from 15 of 32,734 scheduled clinic visits were excluded because the patients had reportedly taken diuretic or antihypertensive medications since the preceding visit.

ceived calcium supplements, although women considered at increased risk at base line were excluded from the study. Another potential complication of maternal calcium supplementation is neonatal hypocalcemia, which may be caused by the suppression of infant parathyroid secretion.³² Although systematic surveillance for neonatal hypocalcemia was not conducted, the proportions of reported cases did not differ between the treatment groups.

The results of this trial contradict those of published meta-analyses of calcium supplementation in pregnancy,¹⁶⁻²⁰ including the most recent, which found an important reduction in systolic and diastolic blood pressure and preeclampsia.²⁰ The number of women in our study was more than twice that in the entire recent meta-analysis, and the dose of calcium administered equaled the highest in previous studies. Most previous studies, moreover, lacked a placebo group^{3-7,12,14,15} or were conducted in women selected because they were at high risk for preeclampsia.^{9,13} One study is difficult to accept because of the elevated rate of preeclampsia (23 percent) in the placebo group and the unlikely observation that all the wom-

en in whom hypertension developed also had proteinuria.⁸ Another trial cited in two preeclampsia meta-analyses^{18,20} did not distinguish preeclampsia from gestational hypertension.³³ The outcomes with respect to preeclampsia and gestational hypertension in the remaining two studies^{10,11} were statistically consistent with those in our trial. Our experience heightens our concern about the proper use of meta-analysis.^{34,35} A large effect indicated by a meta-analysis of relatively small trials has not always been confirmed by subsequent large trials.³⁶ Meta-analyses cannot substitute for large, well-conducted clinical trials.

In summary, supplementation with 2 g of calcium per day did not reduce the incidence of preeclampsia, pregnancy-associated hypertension, or important maternal and perinatal complications of pregnancy in nulliparous women. Moreover, supplementation did not appear to prevent adverse pregnancy outcomes in adolescents or in women with low baseline dietary calcium intakes or urinary calcium excretion. Our results do not support the use of calcium supplementation to prevent preeclampsia in healthy nulliparous women.

TABLE 3. OBSTETRICAL COMPLICATIONS ACCORDING TO TREATMENT GROUP.*

COMPLICATION	CALCIUM GROUP	PLACEBO GROUP
	(N=2295)	(N=2294)
	no. (%)	
Preterm delivery		
<37 wk	248 (10.8)	229 (10.0)
<34 wk	96 (4.2)	86 (3.7)
Post-term delivery (≥42 wk)	77 (3.4)	82 (3.6)
Preterm premature rupture of membranes	108 (4.7)	86 (3.7)
Induction of labor	352 (15.3)	380 (16.6)
Cesarean delivery	366 (15.9)	390 (17.0)
Placental abruption	13 (0.6)	16 (0.7)
Elevated serum aminotransferase values†	25 (1.1)	20 (0.9)
Renal insufficiency‡	21 (0.9)	23 (1.0)
Cerebral hemorrhage or thrombosis	2 (0.1)	2 (0.1)
Disseminated intravascular coagulation	4 (0.2)	2 (0.1)
Urolithiasis		
Confirmed	1 (0.0)	3 (0.1)
Suspected	2 (0.1)	1 (0.0)

*The table includes all the women randomly assigned to a treatment group. Specific definitions of the complications have been given elsewhere.²¹

†This category includes seven women with the HELLP syndrome in the calcium group and two in the placebo group.

‡Renal insufficiency was defined as an increase in serum creatinine of ≥0.5 mg per deciliter (44.2 μmol per liter) over base line.

Supported by the National Institute of Child Health and Human Development under contracts N01-HD-1-3121 through 3126, N01-HD-2-3154, and N01-HD-5-3246, with co-funding from the National Heart, Lung, and Blood Institute.

We are indebted to the members of the Calcium for Preeclampsia Prevention (CPEP) Data Safety and Monitoring Board: Marshall Lindheimer, M.D., Colin Begg, Ph.D., Thomas Chalmers, M.D. (deceased), Maurice Druzin, M.D., Robert Sokol, M.D., and Reginald Tsang, M.B., B.S.; to the CPEP Clinic Coordinators: Lynn Barabach, R.N., Brenda Stofan, R.N., Veronica Dorato, R.N., Teresa Carr, R.N., and Karen McCracken, R.N.; to Heinz Berendes, M.D., Jose Rigau-Perez, M.D., and Jose Villar, M.D., without whom this trial would not have been undertaken; to Donald Stablein, Ph.D., James Knoke, Ph.D., Ms. Donna Brown, Ms. Kate Tomlin, Ms. Martine Thompson, Mr. Warren Pendleton, Robert Kiwi, M.D., Brian Mercer, M.D., Carlene Grim, R.N., Margo Woods, D.Sc., Ms. Ann LaBrode, James Leef, Ph.D., Ms. Nichole Nelson, Ms. Lynn Salo, and Mr. Harvey Shifrin for their assistance; to Glen Hortin, M.D., and Tsunenobu Tamura, M.D., for the analyses of urine calcium and creatinine and of the calcium content of the study tablets; to the Department of Obstetrics and Gynecology at the Lovelace Medical Center for the recruitment and follow-up of CPEP patients; to SmithKline Beecham Consumer Brands for the study tablets; to McNeil Consumer Products Co. for the acetaminophen tablets; to Mission Pharmacal Co. for supplying Mission Prenatal supplements; to Johnson & Johnson-Merck for providing Mylanta; and to Miles, Inc., for providing Ames reagent strips.

TABLE 4. PERINATAL OUTCOME ACCORDING TO TREATMENT GROUP.*

OUTCOME	CALCIUM GROUP	PLACEBO GROUP
	(N=2295)	(N=2294)
Wk of gestation at delivery†	38.9±2.5	38.9±2.4
Birth weight — g‡	3192±611	3218±603
<2500 g — no. (%)	188 (8.8)	205 (9.6)
>4000 g — no. (%)	126 (5.9)	153 (7.2)
Small for gestational age (<10th percentile) — no. (%)	124 (5.8)	105 (4.9)
Birth length — cm†	49.9±3.7	50.0±3.7
Apgar score†		
At 1 min	7.7±1.7	7.8±1.6
At 5 min	8.8±0.9	8.8±0.8
Admission to neonatal intensive care unit — no. (%)†	343 (16.1)	315 (14.7)
Neonatal hypocalcemia — no. (%)‡	36 (1.7)	26 (1.2)
Perinatal losses — no. (%)§	34 (1.5)	36 (1.6)
Induced abortion	2 (0.1)	1 (0.0)
Spontaneous abortion	5 (0.2)	7 (0.3)
Fetal death	15 (0.7)	19 (0.8)
Neonatal death	12 (0.5)	6 (0.3)
Postneonatal death¶	0	3 (0.1)

*Plus-minus values are means ±SD.

†Values are based on all live births: 2134 and 2139 in the calcium and placebo groups, respectively.

‡Hypocalcemia was defined as a serum total calcium concentration of <8.0 mg per deciliter (2.0 mmol per liter), or <7.0 mg per deciliter (1.7 mmol per liter) for infants of <37 weeks' gestation.

§These values are based on data for all the randomized patients.

¶Postneonatal death was defined as death of a newborn infant more than 27 days after birth but before discharge from the hospital.

REFERENCES

- Hypertensive disorders in pregnancy. In: Cunningham FG, MacDonald PC, Gant NF. Williams obstetrics. 18th ed. Norwalk, Conn.: Appleton & Lange, 1989:653-94.
- National High Blood Pressure Education Program Working Group report on high blood pressure in pregnancy. Am J Obstet Gynecol 1990;163:1689-712.
- Theobald GW. Effect of calcium and vitamins A and D on incidence of pregnancy toxemia. Lancet 1937;1:1397-9.
- Nutrition of expectant and nursing mothers: interim report of the People's League of Health. Lancet 1942;2:10-2.
- Chaudhuri SK. Calcium deficiency and toxemia of pregnancy. J Obstet Gynaecol India 1969;19:313-6.
- Montanaro D, Boscutti G, Antonucci F, et al. Prevention of pregnancy-induced hypertension (P.I.H.) and preeclampsia (P.E.) by oral calcium supplementation: preliminary results. Miner Metab Res Italy 1986;7:121-4.
- Marya RK, Rathee S, Manrow M. Effect of calcium and vitamin D supplementation on toxemia of pregnancy. Gynecol Obstet Invest 1987;24:38-42.
- Lopez-Jaramillo P, Narvaez M, Weigel RM, Yopez R. Calcium supplementation reduces the risk of pregnancy-induced hypertension in an Andes population. Br J Obstet Gynaecol 1989;96:648-55.
- Lopez-Jaramillo P, Narvaez M, Felix C, Lopez A. Dietary calcium supplementation and prevention of pregnancy hypertension. Lancet 1990;335:293.
- Villar J, Repke JT. Calcium supplementation during pregnancy may reduce preterm delivery in high-risk populations. Am J Obstet Gynecol 1990;163:1124-31.
- Belizán 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.
12. Ito M, Koyama H, Ohshige A, Maeda T, Yoshimura T, Okamura H. Prevention of preeclampsia with calcium supplementation and vitamin D₃ in an antenatal protocol. *Int J Gynaecol Obstet* 1994;47:115-20.
 13. 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.
 14. Cong K, Chi S, Liu G. Calcium and pregnancy induced hypertension. *Chung Hua Fu Chan Ko Tsa Chih* 1993;28:657-9. (In Chinese.)
 15. Suzuki Y, Itoh Y, Hayashi Y, et al. Calcium supplementation to prevent gestational hypertension. In: Abstract book: 10th World Congress: International Society for the Study of Hypertension in Pregnancy, Seattle, August 4-8, 1996:152. abstract.
 16. Duley L. Prevention and treatment of pre-eclampsia. *Oxford Database of Perinatal Trials Newsletter*. February 1991:2-4.
 17. Levine RJ, Raymond E, DerSimonian R, Clemens JD. Preeclampsia prevention with calcium supplementation. *Clin Appl Nutr* 1992;2:30-8.
 18. Carroli G, Duley L, Belizan JM, Villar J. Calcium supplementation during pregnancy: a systematic review of randomised controlled trials. *Br J Obstet Gynaecol* 1994;101:753-8.
 19. DerSimonian R. Meta-analysis in the design and monitoring of clinical trials. *Stat Med* 1996;15:1237-48.
 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. Levine RJ, Esterlitz JR, Raymond EG, et al. Trial of Calcium for Preeclampsia Prevention (CPEP): rationale, design, and methods. *Control Clin Trials* 1996;17:442-69.
 22. Levine RJ, DerSimonian R. Effects of calcium supplementation on pregnancy-induced hypertension. *JAMA* 1996;276:1387.
 23. Brenner WE, Edelman DA, Hendricks CH. A standard of fetal growth for the United States of America. *Am J Obstet Gynecol* 1976;126:555-64.
 24. Trudeau DL, Freier EF. Determination of calcium in urine and serum by atomic absorption spectrophotometry (AAS). *Clin Chem* 1967;13:101-14.
 25. Hoffman RJ, Feld RD. A modified procedure for creatinine (CRT) which eliminates bilirubin (BILT) interference on the Hitachi 737. *Clin Chem* 1988;34:1313. abstract.
 26. Swanson AF, Swartzentruber M, Nolen PA, Crawford K, Sine HE. Multicenter evaluation of the Boehringer Mannheim compensated, rate-blanked creatinine/Jaffe application on BM/Hitachi systems. In: *Advances in clinical diagnostics*. Indianapolis: Boehringer Mannheim, 1993:3-11.
 27. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic research: principles and quantitative methods*. New York: Van Nostrand Reinhold, 1982:340-55.
 28. Diggle PJ, Liang K-Y, Zeger SL. *Analysis of longitudinal data*. Oxford, England: Oxford University Press, 1994.
 29. Kalbfleisch JD, Prentice RL. *The statistical analysis of failure time data*. New York: John Wiley, 1980.
 30. Heaney RP, Skillman TG. Calcium metabolism in normal human pregnancy. *J Clin Endocrinol Metab* 1971;33:661-70.
 31. Maikranz P, Holley JL, Parks JH, Lindheimer MD, Nakagawa Y, Coe FL. Gestational hypercalciuria causes pathological urine calcium oxalate supersaturations. *Kidney Int* 1989;36:108-13.
 32. Calcium and hypocalcemia. In: Klaus MH, Fanaroff AA, eds. *Care of the high-risk neonate*. 3rd ed. Philadelphia: W.B. Saunders, 1986:227-31.
 33. 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.
 34. Wachter KW. Disturbed by meta-analysis? *Science* 1988;241:1407-8.
 35. Baxter GF, Sumeray MS, Walker JM. Infarct size and magnesium: insights into LIMIT-2 and ISIS-4 from experimental studies. *Lancet* 1996;348:1424-6.
 36. Borzak S, Ridker PM. Discordance between meta-analyses and large-scale randomized, controlled trials: examples from the management of acute myocardial infarction. *Ann Intern Med* 1995;123:873-7.

RECEIVE THE *JOURNAL'S* TABLE OF CONTENTS EACH WEEK BY E-MAIL

To receive the table of contents of the *New England Journal of Medicine* by e-mail every Thursday morning, send an e-mail message to:

listserv@massmed.org

Leave the subject line blank, and type the following as the body of your message:

subscribe TOC-L

You can also sign up through our website at: <http://www.nejm.org>
