

# THE EFFECT OF CALCIUM SUPPLEMENTATION IN THE PREVENTION OF HYPERTENSIVE DISORDERS OF PREGNANCY IN NULLIPAROUS WOMEN

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## ABSTRACT

The purpose of this prospective study was to determine the effect of calcium supplementation in the incidence of hypertensive disorders of pregnancy (gestational hypertension and pre-eclampsia) in nulliparous and high risk women. 300 pregnant women in the 24th week of gestation at the beginning of the study were entered into a double-blind randomized trial. 143 of them who had a positive roll-over test and hypocalciuria at the 28-32nd week of gestation were enrolled for the study.

Subjects were assigned to receive 2 g per day of elemental calcium (52 women) or placebo (61 women) from the 28-32nd week of pregnancy until delivery. Results showed that 11.4% of calcium-treated subjects developed gestational hypertension, compared to 31.2% of the placebo group. The rate of hypertensive disorders of pregnancy was also higher in the placebo group (35.6% vs 11.4%,  $p < 0.01$ ).

### Keyword

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## INTRODUCTION

Pregnancy-induced hypertension, including gestational hypertension and pre-eclampsia, remains a major risk factor for maternal morbidity and mortality.<sup>1,2</sup> The precise factor involved in the pathogenesis of such disorders is unknown, but recent studies have suggested an association with abnormal calcium metabolism.<sup>10,11</sup>

The mechanisms leading to abnormal calcium metabolism in pregnancy-induced hypertension are not currently understood, although decreased urinary calcium levels may play an important role.<sup>5</sup> Several clinical trials have studied the impact of oral calcium supplementation of at least 2g/day during the second half of pregnancy on the incidence of pregnancy-induced hypertension.<sup>3,6,9</sup>

## MATERIALS AND METHODS

Potential candidates for this study were all normotensive nulliparous pregnant women at 24 weeks gestation attending the prenatal clinics of eleven health centers of Mashhad University between April 3, 1995 and November 5, 1995.

Women were considered to have gestational hypertension if measurement of blood pressure on two occasions at least six hours apart revealed an increase of  $\geq 30$  mmHg and  $\geq 15$  mmHg in the systolic and diastolic values, respectively, or a systolic blood pressure  $\geq 140$  mmHg and a diastolic blood pressure  $\geq 90$  mmHg after the 24th week of gestation in the absence of proteinuria, using a zero mercury sphygmomanometer with the patient in the sitting position.

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Table I. Characteristics of the study and control groups.\*

Characteristic	Calcium group (n= 58)	Placebo group (n= 85)
Weeks of gestation (for roll-over test)	29.2±1.26	29.5±1.47
Age(y)	22.1±3.9	22.7±1.2
Weight (kg)	64.2±8.0	60.8±9.3
Weight gain (kg)	4.3±2.3	4.0±2.5
Systolic BP (mmHg)	110.6±11.2	110.7±12.4
Diastolic BP (mmHg)	70.8±14.7	67.6±13.7
MAP (mmHg)	84.0±10.4	81.5±11.9
Serum calcium (mg/dL)	9.38±0.2	10.8±11.5
Serum phosphate (mg/dL)	3.63±0.5	3.56±0.5
B.U.N. (mg/dL)	8.86±2.6	8.74±3.0
Serum uric acid (mg/dL)	3.39±0.5	3.57±0.7
Urinary calcium (g/24h)	82.2±27.9	87.7±22.8
Urinary creatinine (g/24h)	0.89±0.4	0.75±0.3

\*Plus and minus values are mean±SD.

Pre-eclampsia was considered if they met the criteria for gestational hypertension and proteinuria (protein>0.3 g/liter urine) on examination of at least two separate (more than six hours apart) random urine specimens obtained after the 24th week of gestation. Pregnancy-induced hypertension refers to the presence of either pre-eclampsia or gestational hypertension.

Subjects were nulliparous, with singleton pregnancies, 24 weeks gestational age (based on last menstrual period, if the subject had regular menstrual cycles and didn't use oral contraceptive pills prior to conception), blood pressure below 140/90 mmHg, a positive roll-over test (supine diastolic blood pressure  $\geq$ 20 mmHg compared to that obtained on her side) and hypocalciuria (195 mg/24 hours) at 28-32 weeks of pregnancy. Therefore subjects were screened for three risk factors: nulliparity, positive roll-over test and hypocalciuria.

All were free of any underlying medical disorders, determined by a comprehensive physical examination and routine laboratory tests (FBS, serum creatinine, CBC, BUN,

urinalysis), thus 143 pregnant women were screened from 300 women. The women were assigned randomly in a double-blind fashion at 28-32 weeks' gestation to one of two treatment groups. The calcium tablets and placebo were produced solely for this study by the pharmaceutical department of Mashhad university. Each tablet contained calcium gluconate (500 mg of elemental calcium) and granulated starch. The placebo tablets contained lactose and granulated starch and were identical to the calcium tablets with respect to weight, size, flavor and color. Each woman was instructed and continually encouraged to take four tablets per day for a total daily calcium supplementation of 2000 mg in the calcium group. Dietary calcium intake (just dairy products) was estimated by the 24 hour dietary recall method.

Calcium excretion and serum uric acid level were measured at the beginning of the study and at term.

All prenatal care was provided by five trained midwives and one physician. Tablet intake and compliance was assessed at each visit. Outcome data were collected after delivery but

**Table II.** Effect of calcium supplementation on the incidence of hypertensive disorders of pregnancy.

Disorder	Calcium group (n= 52)	Placebo group (n= 61)	P-Value
Gestational hypertension	11.4%(6)	31.2%(19)	<0.01
Pre-eclampsia	0.0%(0)	3.3%(2)*	
P.I.H+	11.4%(6)	35.6%(21)	<0.01

\*not enough for statistical analysis.

+Gestational hypertension and pre-eclampsia.

before the code was broken. All outcome data were accumulated and entered into a computerized data base statistical software package. For analysis of data we used the unpaired Student's t-test, paired t-test, and  $\chi^2$  test. Relative risks (PRs) and their 95% confidence intervals (CIS) were estimated for the main outcome variables.  $P < 0.05$  was regarded as statistically significant.

## RESULTS

Among 300 nulliparous women, 143 subjects with a positive roll-over test and hypocalciuria were considered for follow-up. 85 were assigned to placebo and 58 to calcium. 20% were lost to follow-up.

The study groups were very similar at the time of randomization with respect to several clinical, demographic and biochemical variables (Table I).

The mean ( $\pm$ SD) intake of calcium per day from dairy products during the study was  $480 \pm 249$  mg and  $534 \pm 267$  mg in the calcium and placebo groups, respectively.

The number of tablets taken by the women as determined by pill counts was very similar in both groups; on average, the women in the placebo group took 74 percent of the tablets and the women in the calcium group took 78%.

Data on the frequency of hypertensive disorders of pregnancy in the two groups and the overall treatment effect are shown in Table II.

We used the chi-square test to compare the probability of hypertensive disorders of pregnancy in the two groups.

The incidence of gestational hypertension was 11.4% in the calcium group and 31.2% in the placebo group ( $p < 0.01$ ), while the incidence of pre-eclampsia was 0.0% in the calcium group and 3.3% in the placebo group which was not sufficient for statistical analysis. The overall rates of hypertensive disorders of pregnancy were 35.6% in the placebo group and 11.4% in the calcium group ( $p < 0.01$ ). Determination of the correlation degree between systolic blood pressure and serum calcium value at term in the two groups showed that there was negative correlation in the

placebo group. On the other hand, with a decrease of serum calcium values at term, systolic blood pressure increases at term in the placebo group ( $r = -0.28$ ,  $p = 0.02$ ).

It has previously been suggested that there is an association between calcium supplementation and greater gestational age<sup>7</sup> and lower rates of preterm delivery<sup>13</sup> in high risk populations. In this study, the incidence of birth before 37 weeks of gestation was 2.0% in the calcium group and 5.3% in the placebo group, but this difference was not statistically significant.

Possible side effects and symptoms reported by the subjects including gastrointestinal and neurologic symptoms were monitored during pregnancy. No differences or specific patterns that could be related to treatment status were found.

We observed no statistically significant differences between treatment groups in the distribution of APGAR scores or in any anthropometric variables. The mean birth weight was  $3114.5 \pm 405.7$  g in the calcium group and  $3116.3 \pm 454.4$  g in the placebo group (not significant).

## DISCUSSION

According to our double-blind randomized controlled trial, supplementation with 2g of calcium per day from the 28-32nd week of gestation to term decreases the incidence of hypertensive disorders of pregnancy. Considerable evidence suggests an association between pre-eclampsia and alterations in calcium metabolism that could be mediated by changes in the hormonal regulation of calcium metabolism.<sup>1,8</sup> On the other hand, high calcium intake is associated with increased serum calcium levels,<sup>1</sup> lower parathyroid hormone concentrations, and reduction in renal calcium reabsorption, all of which act to increase urinary calcium excretion as well as lower the blood pressure.<sup>13</sup>

By lowering serum levels of parathyroid hormone, calcium supplementations could reduce intracellular calcium concentrations and therefore lower blood pressure.<sup>2</sup> Our results suggest that calcium supplementation offers protection against PIH in nulliparous, hypocalciuric women

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with a positive roll-over test.

Previous studies have suggested that calcium supplementation may reduce preterm labor, preterm delivery and low birth weight infants.<sup>13</sup> We did not observe a reduction in preterm birth or fetal growth retardation among those patients supplemented with calcium.

No serious side effects or complications were noted in women taking supplemental calcium. The sample size of this study may not have been large enough to rule out the possibility of significant complications such as kidney stones, since the duration of supplementation was short. However, a recent publication suggested that high calcium intake may decrease the risk of symptomatic nephrolithiasis.<sup>9</sup>

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