

# Gestational Calcium Supplementation and Blood Pressure in the Offspring

Daniel C. Hatton, Jane Harrison-Hohner,  
Sarah Coste, Mark Reller, and David McCarron

**Background:** The current study examined the relationship between calcium supplementation during pregnancy and blood pressure (BP) in the mother and offspring at 3 months and at 2 years postpartum.

**Methods:** Nulliparous pregnant women were assigned to either receive 2 g of calcium or placebo daily beginning between weeks 13 to 21 of gestation and continuing until delivery. Blood pressure was measured in children and their mothers at 3 months ( $n = 260$ ) and ( $n = 57$ ) at 2 years postpartum. Systolic BP was measured in the infants using a sphygmomanometer with ultrasonic amplification. For the toddlers, three supine BP measurements were taken from the right arm using a Critikon automated sphygmomanometer just after measurement of left ventricular wall thickness.

**Results:** Systolic BP in the calcium-supplemented infants was 2.2 mm Hg lower than in the placebo group ( $P$

$> .05$ ). At 2 years of age, systolic BP was 4.8 mm Hg lower in the calcium supplemented group ( $P < .05$ ), whereas diastolic BP was 3 mm Hg lower ( $P > .05$ ). There was no difference in left ventricular mass index between groups, although there was a significant correlation between systolic BP and wall thickness ( $P < .05$ ). Maternal BP was positively correlated with circulating  $1,25(\text{OH})_2\text{D}_3$  ( $P < .001$ ) but did not differ between calcium groups at 3 months postpartum.

**Conclusions:** The data on BP in the children are in agreement with previous studies and argue strongly for additional research into the effects of prenatal calcium supplementation on BP regulation in the offspring. Am J Hypertens 2003;16:801–805 © 2003 American Journal of Hypertension, Ltd.

**Key Words:** Dietary calcium, pregnancy, blood pressure, infant, calcitriol, parathyroid hormone.

There are reports that prenatal calcium supplementation may have a lasting impact on blood pressure (BP) in the offspring. Belizan et al<sup>1</sup> reported that offspring of mothers who were supplemented with 2 g of calcium per day during the latter half of gestation had lower BP than those in the placebo group. The effect was most pronounced in children that were overweight. Similarly, McGarvey et al<sup>2</sup> found that infants born to mothers with high calcium diets had lower BP than those on low calcium diets. More recently, Bergel and Belizan<sup>3</sup> found that offspring born to rat dams on a deficient calcium diet had significantly higher BP than normal or calcium-supplemented offspring. The difference in BP was greatest at termination of the study at 52 weeks postpartum.

Together, the data suggest that prenatal calcium supplementation may be capable of programming fetal BP. To test that hypothesis, the current study examined BP in the

infants and toddlers of mothers who participated in a clinical trial of calcium supplementation during pregnancy. It was hypothesized that calcium supplementation during gestation would result in lower BP in the offspring.

## Methods

Blood pressure data was collected as part of a follow-up study<sup>4</sup> to the Calcium for Prevention of Preeclampsia Trial (CPEP).<sup>5</sup> CPEP was a multicenter, randomized, placebo-controlled clinical trial that tested whether calcium supplementation during pregnancy would reduce the incidence of preeclampsia in a population of healthy, young, nulliparous women. In that trial, women were assigned to either receive 2 g of calcium or placebo daily beginning between weeks 13 and 21 of gestation and continuing to term when calcium supplementation was discontinued.

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From the Departments of Behavioral Neuroscience (DCH, JH-H, SC), Molecular Microbiology and Immunology (SC), Pediatrics (MR), and Medicine, Division of Nephrology (DCH, DM), Oregon Health & Science University, Portland, Oregon and Department of Nutrition (DM), University of California at Davis, Davis, California.

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Address correspondence and reprint requests to Dr. Daniel C. Hatton, Department of Behavioral Neuroscience, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239-3098; e-mail: hatton@ohsu.edu

**Table 1.** Blood pressure and cardiac index

Variable	Calcium	n	Placebo	n
Maternal SBP 3 months (mm Hg)	103.4 ± 11.5	134	103.6 ± 11	131
Maternal DBP 3 months (mm Hg)	64.3 ± 9.1	134	65.4 ± 8.9	131
Infant SBP (mm Hg)	111.4 ± 14.3	130	113.6 ± 12.6	130
Maternal SBP 2 y (mm Hg)	101.9 ± 12.9	37	104.1 ± 9.6	25
Maternal DBP 2 y (mm Hg)	67.1 ± 7.7	37	67.8 ± 8.2	25
Toddler SBP (mm Hg)	95.4 ± 7.6*	35	100.2 ± 7.9	18
Toddler LV mass index (g/m <sup>2</sup> )	49.7 ± 8.7	35	50.2 ± 5.9	18

DBP = diastolic blood pressure; LV = left ventricular; SBP = systolic blood pressure.

Values are means ± SD.

\* denotes significance at  $P < .05$ .

## Study Population

The current study was limited to participants from the Portland, Oregon center. Subjects were eligible for participation if they had: 1) completed the CPEP protocol, 2) delivered an infant without serious health problems, and 3) an ability to read English. Subjects were contacted by telephone and invited to participate in the follow-up study at 12 weeks postpartum or when the child was 2 years of age. Women who agreed to participate were seen along with their child.

After completing the informed consent form approved by the Institutional Review Board at Oregon Health Sciences University, the subjects completed a detailed questionnaire concerning medical, obstetric, psychiatric, and contraceptive histories, lactation status, and demographic variables. Maternal height and weight were measured along with two sitting BP measurements. A 30-mL blood sample was taken from the antecubital vein for measurement of calcium-regulating hormones at 3 months postpartum.

Systolic BP was measured in 3-month-old infants using a sphygmomanometer with ultrasonic amplification (Parks Electronics, Beaverton, OR) and an infant-sized cuff. Three measurements were taken of BP separated by 1-min intervals. Infant BPs were standardized to the right arm in a supine position.

For the toddlers, three supine BP measurements were taken from the right arm using a Critikon automated sphygmomanometer just after measurement of left ventricular wall thickness. Left ventricular wall mass was measured using standard M-mode images obtained from two-dimensional echocardiography. The measurements of left ventricular internal dimension, septal, and posterior wall thickness were taken at end-diastole using the method established by the American Society of Echocardiography.<sup>6</sup> The toddlers were lying comfortably in a supine position with images obtained from the parasternal position. The scan took about 5 min.

## Assays

Serum levels of 1,25(OH)<sub>2</sub>D<sub>3</sub> in maternal serum were determined using a commercially available radioimmuno-

assay kit (Nichols Institute, San Juan Capistrano, CA), as were levels of intact parathyroid hormone (Allegro intact PTH, Nichols Institute, Diagnostics) and calcitonin (Instar, Stillwater, MN).

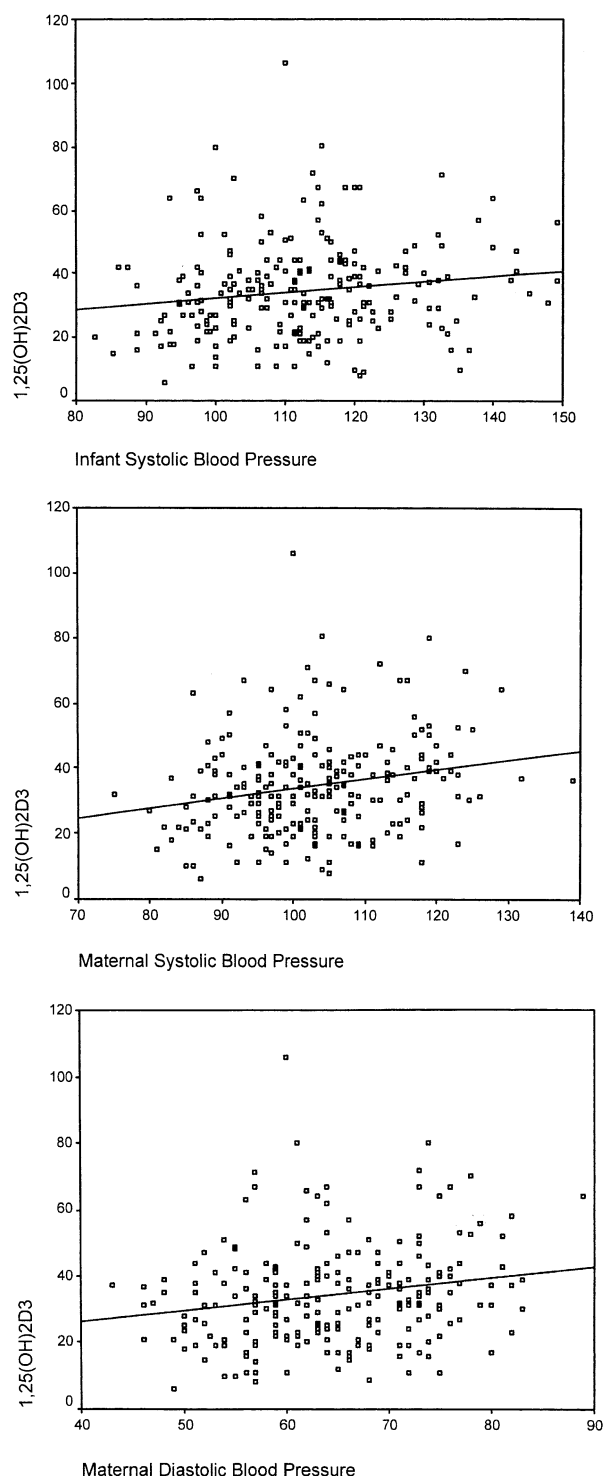
## Data Analysis

The measurement of left ventricular mass was calculated using the equation reported by Devereux and validated against anatomic measurements.<sup>7</sup> This method has been used successfully in investigations involving children.<sup>8</sup> Comparisons between groups were done with *t* tests. Chi-square was used to assess proportional data. Pearson correlation coefficients and partial correlations were used to assess the relationship between calcium-regulating hormones and BP. A probability  $< .05$  was used to determine statistical significance. Comparisons between treatment groups were performed by the EMMES Corporation (Rockville, MD) allowing the investigators to remain blinded to the treatment condition of the women.

## Results

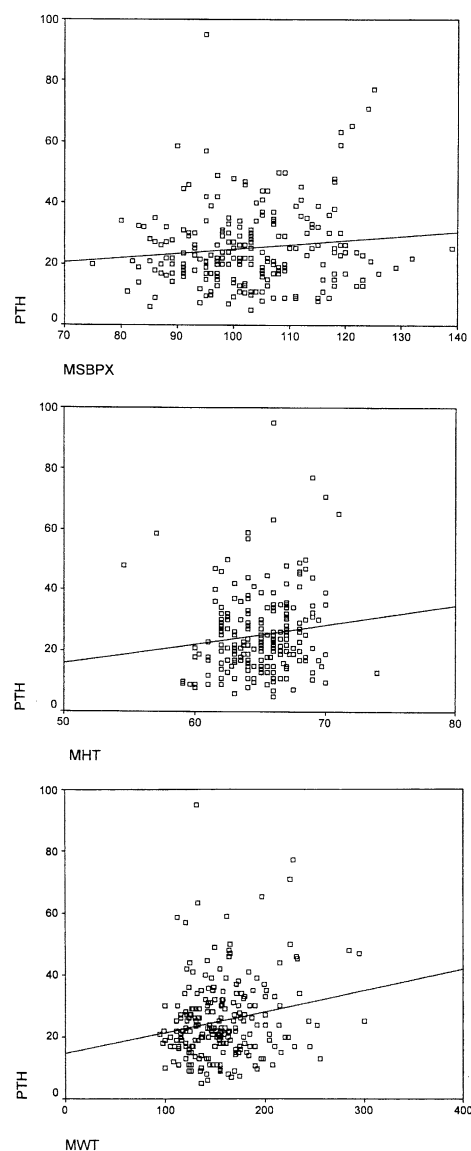
Of the 497 CPEP subjects invited to participate in the follow-up study, BP was measured in 260 infants at 3 months of age and 57 toddlers at 2 years of age. Blood pressure data in the mothers and infants are presented in Table 1. There was no difference in BP between maternal calcium and placebo groups at either time point. Systolic BP in the calcium-supplemented infants was 2.2 mm Hg lower than in the placebo group ( $P > .05$ ). At 2 years of age, systolic BP was 4.8 mm Hg lower in the calcium-supplemented group ( $P < .05$ ), whereas diastolic BP was 3 mm Hg lower ( $P > .05$ ). There was no difference in left ventricular mass index between the calcium supplemented and placebo children at 2 years of age.

Maternal systolic ( $r = 0.235$ ) and diastolic BP ( $r = 0.223$ ) were significantly correlated with 1,25(OH)<sub>2</sub>D<sub>3</sub> ( $P < .001$ ). The regression lines are shown in Fig. 1. Infant systolic BP was also significantly correlated with maternal 1,25(OH)<sub>2</sub>D<sub>3</sub> ( $r = 0.17$ ,  $P < .05$ ). The relationship between 1,25(OH)<sub>2</sub>D<sub>3</sub> and maternal BP was independent of lactation status. In the infant, 1,25(OH)<sub>2</sub>D<sub>3</sub> was signifi-



**FIG. 1.** Scattergrams of the relationship between  $1,25(\text{OH})_2\text{D}_3$  and blood pressure in the mother and infant at 3 months postpartum ( $n = 260$ ). (**Top Panel**) Infant systolic blood pressure and  $1,25(\text{OH})_2\text{D}_3$ ,  $r = 0.17$ ,  $P < .05$ ; (**Middle Panel**) maternal systolic blood pressure and  $1,25(\text{OH})_2\text{D}_3$ ,  $r = 0.235$ ,  $P < .001$ ; (**Bottom Panel**) maternal diastolic blood pressure and  $1,25(\text{OH})_2\text{D}_3$ ,  $r = 0.223$ ,  $P < .001$ .

cantly correlated with BP for those that were breast-fed at least through 6 weeks ( $r = 0.20$ ,  $n = 123$ ,  $P < .05$ ), but was not significant for those not breast-fed ( $r = 0.10$ ,  $n =$



**FIG. 2.** Scattergrams of the relationship between parathyroid hormone (PTH) and maternal systolic blood pressure, height, and weight in women that were breast feeding at 6 weeks postpartum ( $n = 124$ ). (**Top Panel**) Maternal systolic blood pressure (MSBPX) and PTH,  $r = 0.228$ ,  $P < .05$ ; (**Middle Panel**) maternal height (MHT) and PTH,  $r = 0.362$ ,  $P < .001$ ; (**Bottom Panel**) maternal weight (MWT) and PTH,  $r = 0.352$ ,  $P < .001$ .

105,  $P > .05$ ) through 6 weeks. There was no significant correlation between maternal BP and infant systolic BP ( $r = 0.07$ ,  $P > .05$ ). There was, however, a significant correlation between maternal diastolic pressure and mean BP in the toddlers ( $r = 0.373$ ,  $P = .004$ ).

Parathyroid hormone was significantly related to maternal systolic BP ( $r = 0.228$ ,  $P < .05$ ), maternal height ( $r = 0.362$ ,  $P < .001$ ), and weight ( $r = 0.352$ ,  $P < .001$ ) in women that were lactating at 6 weeks. The regression lines are shown in Fig. 2. After controlling for height and weight, there was no longer a significant relationship between PTH and maternal systolic BP ( $r = 0.10$ ,  $P > .05$ ). In contrast, the correlation between  $1,25(\text{OH})_2\text{D}_3$  and ma-

ternal systolic ( $r = 0.182$ ,  $P = .006$ ) and diastolic ( $r = 0.170$ ,  $P = .010$ ) BP remained significant after controlling for height and weight.

After controlling for infant or toddler height, weight, gender, and breast-feeding status, the correlation between birth weight and BP was not significant at either 3 months ( $r = -0.05$ ,  $P > .05$ ) or 2 years of age ( $r = -0.03$ ,  $P > .05$ ). The correlation between current weight and systolic pressure was not significant ( $r = -0.006$ ,  $P > .05$ ) in the infant but was in the toddlers ( $r = 0.283$ ,  $P < .05$ ).

Left ventricular mass was significantly correlated with body height ( $r = 0.415$ ,  $P < .001$ ) and weight ( $r = 0.631$ ,  $P < .001$ ), whereas left ventricular mass index was significantly associated with systolic BP in the toddlers ( $r = 0.295$ ,  $P < .05$ ).

## Discussion

The major finding of the current study was that calcium supplementation during pregnancy resulted in lower BP in the offspring at 2 years of age. This outcome supports the findings of Belizan et al,<sup>1</sup> who found that calcium supplementation during gestation was associated with lower systolic BP in the offspring at a mean age of 7 years (range, 5 to 9 years of age). In that study, the effect was limited to those children who were above the median for weight. In the current study, there were a limited number of subjects at 2 years of age. Consequently, it was not possible to categorize subjects by weight to examine the possibility that calcium may have had a larger effect in heavier children.

The data are also commensurate with those of McGarvey et al,<sup>2</sup> who observed an inverse relationship between dietary calcium intake by the mother during pregnancy and BP in the infant at 1, 6, and 12 months postpartum. In that trial, age-specific infant BP differences between the upper and lower quartiles of maternal prenatal calcium intakes ranged from 3 to 7 mm Hg.

A prenatal effect of calcium on BP is in agreement with postnatal effects of dietary calcium on BP in children. Gillman et al<sup>9</sup> found an inverse association between dietary calcium intake and BP in 3- to 6-year-old children, whereas Simons-Morton et al<sup>10</sup> observed a similar relationship in 8- to 11-year-old children. In a supplementation study, Gillman et al<sup>11</sup> found that fifth graders supplemented with 600 mg of calcium for 12 weeks had a significant decrease in systolic BP that was most pronounced in those with the lowest baseline calcium intakes.

The unique aspect of prenatal calcium supplementation is the time frame of action. In the current study, calcium supplementation stopped at term. The same was the case in the Belizan et al<sup>1</sup> study, yet the BP effects in both studies were apparent years later. These outcomes strongly suggest that calcium may influence fetal programming of BP. There is ample evidence that nutrition during gestation can have a lasting impact on BP. The seminal report of Barker et al<sup>12</sup> on an inverse relationship between birth weight and

BP in adulthood has led to a multitude of studies that have reported an inverse relationship between birth weight and BP from childhood through old age.<sup>13</sup>

There was no significant relationship between birth weight and BP in the current study, nor was there in the Belizan et al<sup>1</sup> study, suggesting that supplemental calcium may influence BP independently of birth weight. It is possible that dietary calcium influences programming of BP through calcium-regulating hormones. There is indirect evidence that aspects of the calcium-regulating system may be programmed in utero. Dennison et al<sup>14</sup> found that low birth weight predicted low bone mineral density in elderly women. Subsequently, Arden et al<sup>15</sup> reported an inverse relationship between birth weight and both circulating  $1,25(\text{OH})_2\text{D}_3$  and fractional intestinal strontium absorption, an index of calcium absorption in the gut. These results suggest the possibility that some aspect of the calcium-regulating system involving  $1,25(\text{OH})_2\text{D}_3$  may be programmed in utero in response to nutrition.

Calcium-regulating hormones have been reported to play a role in the BP response to calcium supplementation.<sup>16</sup> Both  $1,25(\text{OH})_2\text{D}_3$  and PTH are vasoactive hormones that influence BP. However, the relationships are complex and not well understood. Calcitriol is known to be a vasoconstrictor,<sup>17,18</sup> yet is often found to be inversely related to BP.<sup>19,20</sup> In contrast, PTH is a potent vasodilator<sup>21</sup> that is frequently found to be associated with an elevation in BP.<sup>22–24</sup>

In the current study, both  $1,25(\text{OH})_2\text{D}_3$  and PTH were significantly and positively related to BP in the mother. However, PTH was significantly related to BP only in women who were lactating. Moreover, it appeared that the relationship between PTH and BP may have been mediated through body size. When height and weight were controlled for, there was no longer a significant association between PTH and BP. In contrast, the relationship between  $1,25(\text{OH})_2\text{D}_3$  and BP was independent of body size and lactational status. There was no relationship between calcium-regulating hormones and supplemental status during pregnancy.

There was a significant relationship between maternal  $1,25(\text{OH})_2\text{D}_3$  and BP in infants who were nursing. The basis for that relationship is not clear. It seems unlikely that this relationship was a consequence of maternal  $1,25(\text{OH})_2\text{D}_3$  levels acting on infant  $1,25(\text{OH})_2\text{D}_3$  levels, as there is little correlation between maternal and infant  $1,25(\text{OH})_2\text{D}_3$  levels.<sup>25</sup> It also seems unlikely that the relationship is a consequence of elevated  $1,25(\text{OH})_2\text{D}_3$  levels in the nursing infants, as  $1,25(\text{OH})_2\text{D}_3$  levels are not different between formula-fed and breast-fed infants.<sup>26</sup> Additional research will be needed to clarify the relationship between maternal  $1,25(\text{OH})_2\text{D}_3$  and infant BP.

In summary, the data suggest that calcium supplementation during pregnancy may have a lasting effect on the BP of the offspring. These outcomes have important implications for public health and provide further evidence of the importance of prenatal nutrition on the programming

of BP. The implications of the data need to be tempered by the limitations of the current study. The study was not designed or powered to examine BP in the offspring. The number of participants at 2 years of age, when the effect of calcium on BP was significant, was relatively small, making the outcomes less reliable. Nevertheless, the data are in agreement with previous studies<sup>1,2</sup> and the outcomes are strengthened by the randomized design of the trial and the blinded measurement and analysis of BP. All things considered, the data argue strongly for additional research into the effects of prenatal calcium supplementation on BP regulation in the offspring.

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