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Original article

Effect of calcium supplementation on maternal hypertensive disorders and neonatal outcomes among pregnant Thai women: A 2-year interim analysis report

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Background: Calcium intake is inversely correlated with hypertensive disorder in pregnancy. The amount of daily calcium intake varies by country. Therefore, the effect of calcium supplementation may be different.
Objectives: The primary outcome was to evaluate the effect of calcium supplementation in hypertensive disorder in pregnant Thai women. Secondary outcomes were to evaluate the side effects of calcium supplementation and the effects on delivering small for gestational age infants.
Methods: One hundred and sixty-two Thai women who visited the antenatal care (ANC) Clinic, King Chulalongkorn Memorial Hospital were enrolled. Patients were randomly allocated to Group A received ferrous sulfate (200 mg) and calcium carbonate (2 grams) per day. Group B received ferrous sulfate (200 mg) per day. Daily calcium intake from food and side effects of calcium supplementation were recorded. Maternal hypertensive disorders, neonatal morbidity, birth weight, and neonatal intensive care unit (NICU) admission were recorded and evaluated. The interim analysis was planned at a two year interval.
Results: The baseline characteristics were similar. Hypertension in pregnancy and delivery outcomes were not different between both groups. Approximately half of the subjects received calcium had constipation (45.7%), bloating (19.8%) and nausea (12.4%).
Conclusion: At the 2-year interval analysis, no risk reduction effects were observed for either hypertensive disorder in pregnancy or for delivering small for gestational age infants. More than half of all calcium supplementation participants experienced side effects from calcium supplementation treatment such as constipation, bloating and nausea.

Keywords: Calcium, hypertension in pregnancy, side effect, small for gestational age.

Hypertensive disorder in pregnancy is an important cause of maternal and neonatal morbidity and mortality.[1, 2] Hypertensive disorder in pregnancy comprises gestational hypertension, preeclampsia, and eclampsia (preeclampsia with convulsion).[3] The overall incidence of hypertensive disorder in pregnancy is approximately 2 - 8%, with rates varying by population.[4 - 8] Hypertensive disorder in pregnancy results in 10 - 15% of all direct maternal mortality and is believed to cause long-term sequelae, such as chronic hypertension and cardiovascular disease. [2, 9,10] Hypertensive disorder in pregnancy also associates with preterm labor (10%), intrauterine growth restriction (12%), and perinatal death (2.7%). [11 - 13] Preterm delivery and intrauterine growth restriction increase the risk of several neonatal complications, including respiratory distress syndrome, seizure, intracranial hemorrhage, hypoglycemia, and prolonged hospitalization.[14]

Calcium intake and intravascular calcium levels were shown in several studies to have an inverse

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relationship with the development of hypertensive disorder in pregnancy. [15, 16] It has been hypothesized that low serum calcium may increase blood pressure by stimulating parathyroid hormone and renin release, which induces an incremental in intracellular calcium in vessels that results in vasoconstriction and hypertension. A Cochrane review reported that calcium supplementation during pregnancy can help reduce the incidence of preeclampsia and gestational hypertension. With high-dose calcium supplementation (1.5 - 2 grams per day), the incidence of preeclampsia was reduced by 55% (relative risk (RR): 0.45 [95% CI: 0.31 - 0.65]) and the incidence of gestational hypertension was reduced by 35% (RR: 0.65 [95% CI: 0.53 - 0.81])-. [3] Imdad A, *et al*. reported that calcium supplementation in pregnant women in developing countries can reduce the incidence of preeclampsia by 59% (RR: 0.41 [95% CI: 0.24 - 0.69]), and that calcium supplementation was associated with a 45% reduction in risk of gestational hypertension (RR: 0.55 [95% CI: 0.36 - 0.85]). Calcium supplementation during pregnancy was also associated with a significant reduction in neonatal mortality (RR: 0.70 [95% CI: 0.56 - 0.88]) and preterm birth (RR: 0.88 [95% CI: 0.78 - 0.99]). [9, 17]

Most currently published evidence supports the hypothesis that calcium supplementation during pregnancy is associated with risk reduction of hypertensive disorder in pregnancy. [3, 17 - 19] However, the amount of daily calcium intake varies by country, culture, geographic area, and eating habits. Daily calcium intake (mg/person/day) ranges from 1,100 mg of daily elemental calcium in the USA, to 884 mg in Israel, 345 mg in Jamaica and 266 mg in Thailand.[16] It is a matter of fact that main food sources of calcium in most countries in North America and Europe are from milk and other dairy products, canned fish, and calcium-fortified foods. Dairy products are not a staple food in Thailand, especially for people living in rural areas. However, daily calcium intake in pregnancy may be different from non-pregnant women due to maternal concerns about the growing baby in the womb.[20] Moreover, routine calcium supplementation in normal pregnant women is not the standard of care in Thailand. As such, an estimation of daily calcium intake in non-pregnant women may not be accurately generalizable to pregnant women – particularly those living in Thailand or other Southeast Asian countries. It is, therefore, possible that calcium supplementation using the previously recommended dosage may yield different outcomes in different regions.

The primary objective of this study was to investigate the effects of calcium supplementation on maternal hypertensive disorders in pregnant Thai women and the secondary outcomes were to evaluate the side effects of calcium supplementation and the effects on delivering small for gestational age infants.

Methods

The protocol for this randomized controlled study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University. One thousand and eight pregnant Thai women who visited King Chulalongkorn Memorial Hospital for antenatal care (ANC) were invited to enroll. Pregnant women aged older than 18 years at the first visit date, with gestational age of 12 weeks or less at the first visit, and who intended to deliver at King Chulalongkorn Memorial Hospital were included.

Patients with a history of hypercalcemic status, including abnormal parathyroid gland function, malignancy, Vitamin-D metabolic disorders, any disorders related to high bone-turnover rates, renal failure, or hypercalcemia from other causes were excluded. Patients with hypocalcemic status, including parathyroid hormone [PTH] deficiency or malfunction, vitamin D deficiency, hypermagnesaemia or hypomagnesaemia, or pregnant women with chronic hypertension or blood pressure more than 140/90 mmHg before the gestational age of 12 weeks were also excluded. Final exclusion conditions included patients with malnutrition and patients receiving calcium supplementation from other sources.

The sample size was calculated by using risk reduction data reported in a previous study. [3] Using an alpha level of 0.05 and a beta level of 0.2, a sample size of 504 subjects was required for each group. We planned to collect all 1008 subjects in a 4-year duration and an interim analysis at a 2-year interval was planned. This study contains preliminary analysis of the data collected during October 2012 and October 2014. This study would be terminated if one arm was exaggeratedly improved compared to the other. However, in case the benefit or risk was not outstanding, the trial should be continued until the full protocol was completed.

All study candidates were counseled regarding the trial protocol, the objectives of the study, and their right to withdraw at any time without any detrimental effect to their continued care. Written informed consent was then obtained from all interested participants prior to inclusion. Demographic and clinical data, including age, occupation, income, weight, height, gravida, parity, underlying disease, and previous pregnancy complications, were collected. Participants were divided into two groups using a random number table. Patients who were randomly allocated to Group A (treatment group) received ferrous sulfate 200 mg and calcium carbonate 2 grams per day (1 gram per tablet per dose) starting from gestational age of 20 weeks until delivery. Patients who were randomly allocated to Group B (control group) received only ferrous sulfate 200 mg per day from gestational age of 20 weeks until delivery. Study participants were asked to record daily dietary intake of high calcium foods like milk, yogurt, and canned fish. All subjects were followed until delivery. Delivery method, outcome, and complications, such as hypertensive disorder in pregnancy, postpartum hemorrhage, and ICU/NICU admission, were recorded. Neonatal outcomes, such as gestational age, birth weight, and APGAR scores, were also collected and recorded. Hypertensive disorder in pregnancy was defined as gestational hypertension, preeclampsia, and/or eclampsia according to World Health Organization (WHO) classifications.[4] Small for gestational age was defined as birth weight less than the 10th percentile of a given gestational age.

Statistical analysis

Baseline demographic and clinical data, and amount of daily milk and/or dairy product intake were compared between groups. Outcomes including hypertensive disease in pregnancy, neonatal morbidity, birth weight, and NICU admission were also compared between groups. General characteristic data were analyzed in mean, mode, median and standard deviation (SD) and presented in tables. As for comparison data, parametric and non-parametric data were analyzed using appropriate statistical methods. Data were analyzed using SPSS Statistics version 17.0 (SPSS, Inc., Chicago, IL, USA). *P*-values of less than 0.05 were regarded as being statistically significant. The interim analysis was planned at the 2 year interval for the analysis of the efficacy of calcium supplements.

Results

The interim analysis at the 2-year interval was performed. The data of all participants who delivered before the end of October 2014 were collected and analyzed. Eighty-one subjects who were allocated to Group A and 81 patients who were assigned to Group B were analyzed. Most baseline demographic and clinical characteristics were not different between the groups. However, the mean weight of Group B participants was statistically significantly higher than that of patients in Group A (58.28 *vs.* 54.13 kg; $P = 0.007$). Moreover, mean baseline diastolic blood pressure in Group B was statistically significantly higher than in Group A (68.32 *vs.* 65.59; $P = 0.04$). Details of baseline characteristics of both groups are given in Table 1.

Regarding calcium supplementation compliance in Group A, 27.16% (22/81) of patients took calcium supplements as assigned (2 grams per day, 14 tablets per week), 64.2% (52/81) took 7 - 14 tablets per week, 6.17% (5/81) took less than 7 tablets per week, and data were incomplete in 2.47% (2/81) of patients. Side effects of calcium supplementation were also evaluated. More than half of subjects experienced side effects from supplemental calcium intake (53.09%; 43/81). The most common side effect was constipation (45.68%; 43/81), followed by bloating (19.75%; 16/81) and nausea (12.35%; 10/81).

For daily dairy products consumption, the subjects from both groups drank 14 glasses of milk per week which was higher than usual Thai people consumption. All delivery records were collected and recorded. There were no statistically significant differences between the groups for gestational age at delivery time, birth weight, APGAR score, mode of delivery, delivery complications (e.g., hypertensive disorder in pregnancy), and NICU admissions. Neonatal low birth weight was also not significantly different between groups. Delivery data of both groups are presented in Table 2.

Discussion

This preliminary analysis found that calcium supplementation in pregnancy did not show noticeable risk reduction effects on hypertensive disorder in pregnancy, including gestational hypertension, mild preeclampsia, and severe preeclampsia. The effect of calcium supplementation on risk reduction for delivery of small for gestational age (SGA) infants was also not shown. However, the final results of the study have to be evaluated after the final report is completed. In the aspect of risk reduction for SGA infants, subgroup analysis may be required. Over half of those who received calcium supplements experienced side effects, with most experiencing constipation. However, no participant reported leaving the study due to side effects (Table 1).

Table 1. Baseline characteristics of study participants.

Characteristics	Group A (n = 81)	Group B (n = 81)	*P* - value
Age (year)	29.5 ± 5.0	30.2 ± 5.0	0.37
Weight (kg)	54.1 ± 7.4	58.3 ± 11.6	0.007
Height (cm)	157.2 ± 6.4	158.1 ± 5.5	0.36
BMI (kg/m^2)	22.0 ± 3.4	23.3 ± 4.0	0.03
GA at 1st ANC (week)	8.6 ± 2.3	8.5 ± 1.9	0.74
Systolic BP (at 1st ANC) [mmHg]	112.6 ± 11.3	115.8 ± 12.0	0.08
Diastolic BP [mmHg]	65.6 ± 8.0	68.3 ± 8.4	0.04
Education [n (%)]			
Less than bachelor degree	48.0 (59.3)	62.0 (76.5)	0.118
Bachelor degree	29.0 (35.8)	16.0 (19.8)	
Master degree or higher	2.0 (2.5)	1.0 (1.2)	
Unknown	2.0 (2.5)	2.0 (2.5)	
Income (Thai baht/month) [n (%)]			
< 10,000 (300 USD)	2.0 (2.5)	5.0 (6.2)	0.55
10,001 - 20,000 (301 - 600 USD)	20.0 (24.7)	24.0 (29.6)	-
20,001 - 50,000 (601-1500 USD)	47.0 (58.0)	45.0 (55.6)	-
> 50,000 (1,500 USD)	11.0 (13.6)	5.0 (6.2)	-
Unknown	1.0 (1.2)	2.0 (2.5)	-
ANC data [n (%)]			
Complication during ANC	58.0 (71.6)	58.0 (71.6)	0.96
Thalassemia trait	31.0 (38.3)	22.0 (27.2)	0.31
Teenage pregnancy	3.0 (3.7)	1.0 (1.2)	0.62
Elderly gravida	17.0 (21.0)	19.0 (23.5)	0.85
GDM	9.0 (11.1)	14.0 (17.3)	0.37
Excessive weight gain	18.0(22.2)	16.0 (19.8)	0.85
Obesity	1.0 (1.2)	9.0 (11.1)	0.02
Preterm	1.0 (1.2)	3.0 (3.7)	0.62
Milk/week (glass)	15.0 ± 5.5	14.5 ± 6.3	0.63

P - value < 0.05 indicates statistical significance. The data are expressed as mean ± SD. ANC: Antenatal care; BMI: Body mass index; BP: Blood pressure; GA: General anesthesia; GDM: Gestational diabetes; USD: US dollars.

Several studies have investigated prevention of hypertensive disorder in pregnancy, especially preeclampsia using low-dose aspirin, calcium, and other nutritional supplements. [4, 16 - 18] Some studies found that calcium supplementation reduced the risk of hypertensive disorder in pregnancy, especially in countries with low calcium intake.

It has long been a rule of thumb to recommend that pregnant women drink more milk or take calcium supplementation to ensure adequate calcium intake to meet maternal and fetal demand. Whether this general recommendation is suitable for all populations of pregnant women still needs to be confirmed. Adequate calcium intake is generally accepted as being an important component for the health of both non-pregnant and pregnant women. However, we have no information or findings that conclusively establish that calcium is an essential determining factor for reducing the risk of hypertensive disorder in pregnancy, delivery of small for gestational age infants, and/or other pregnancy outcomes. If it can be conclusively established that calcium supplementation reduces the risk of these conditions, a national guideline could be established that would mandate calcium supplementation or adequate calcium intake from food sources for all pregnant women. In such a case, the medical benefits would be substantial for mothers and infants and the national healthcare cost savings would be vast.

Table 2. Delivery data of study participants.

	Group A (n = 81)	Group B (n = 81)	*P* - value
GA at delivery (week)	38.1 ± 1.7	38.0 ± 1.7	0.52
Birth weight (gram)	3,083.1 ± 536.9	3,150.2 ± 475.5	0.40
Route of delivery [n (%)]			
Normal labor	48.0 (59.3)	43.0 (53.1)	0.50
Vacuum extraction	1.0 (1.2)	0 (0)	-
Forceps extraction	3.0 (3.7)	2.0 (2.5)	-
Cesarean section	29.0 (35.8)	36.0 (44.4)	-
Labor complication [n (%)]	18.0 (22.2)	22.0 (27.2)	0.59
HT in pregnancy	6.0 (7.4)	6.0 (7.4)	0.56
Gestational HT	2.0 (2.5)	2.0 (2.5)	-
Mild preeclampsia	3.0 (3.7)	1.0 (1.2)	-
Severe preeclampsia	1.0 (1.2)	3.0 (3.7)	-
Non-reassuring FHS	3.0 (3.7)	5.0 (6.2)	0.46
Preterm	10.0 (12.4)	11.0 (13.6)	0.58
PPH	0.0	2.0 (2.5)	0.22
ICU admission	1.0 (1.2)	5.0 (6.2)	0.23
Newborn outcome [n (%)]			
AGA	69.0 (85.2)	68.0 (84.0)	0.66
SGA	4.0 (4.9)	2.0 (2.5)	-
LGA	8.0 (9.9)	11.0 (13.6)	-
LBW (< 2,500 g)	9.0 (11.1)	5.0 (6.2)	0.54
Macrosomia (> 4,000 g)	4.0 (4.9)	3.0 (3.7)	0.93

P - value < 0.05 indicates statistical significance. The data are expressed as mean ± SD. GA: Gestational age; HT: Hypertension; FHS: Fetal heart sound; PPH: Primary postpartum hemorrhage; AGA: Approximate gestational age; SGA: Small for gestational age; LGA: Large for gestational age; LBW: Low birth weight.

The results of this study, though preliminary, indirectly indicate several points that should be considered by healthcare policymakers. First, the calcium supplementation dosage may need to be higher in order to observe an identifiable effect size. Moreover, the cost-benefit of such an increase needs to be weighed against a potential increase in side effects. At a dose of 1 - 2 grams per day, over half of women in this study complained of side effects – particularly constipation. Given that constipation is common during pregnancy; higher dosage calcium supplementation could worsen the condition. Moreover, calcium supplementation in this study showed no effect on other pregnancy outcomes, including gestational age at delivery and birth weight. It is, therefore, recommended that a thorough analysis of the cost-effectiveness of calcium supplementation in pregnant women be undertaken prior to establishing a general recommendation regarding calcium supplementation in pregnancy nationwide.

The strength of this trial is the study design. This randomized controlled trial evaluated the effects of calcium supplementation, with provisions made to accurately record supplementation compliance and calcium intake from food-based sources. Daily dietary calcium intake was recorded by participants in both the calcium supplementation and non-supplementation groups. Side effects in the supplementation group were recorded and analyzed. Li K, *et al*. found and reported that excessive calcium supplementation may be harmful. [21] However, the evidence of harm from excessive calcium remains inconclusive. Based on calcium supplementation side effect data, counseling should be given to patients regarding potential side effects prior to prescription in routine clinical practice. Regarding the compliance of calcium intake in this study, more than 90% of participants took at least 1 gram of additional calcium per day, which was considered adequate compliance for evaluation.

Regarding prevention of hypertensive disorder in pregnancy, this study was not able to identify any difference in incidence between calcium supplementation and no calcium supplementation. This finding is similar to the finding of a study by Goldberg GR, *et al*. [22] They studied calcium supplementation in pregnant Gambian women – a population with a normally low calcium diet (300 - 400 mg per day). They also were not able to identify differences in maternal blood pressure or hypertensive disorder in pregnancy between the calcium supplementation and non-supplementation groups. From their study, they assumed that Gambian women were adapted to low dietary calcium intake, obesity, tobacco use, alcoholic consumption, and excessive weight gain during pregnancy. [22]

While international recommendations for calcium intake range from 700 – 1,000 mg of calcium per day, it was reported that non-pregnant Thai women consume only 266 mg of calcium per day.[15] However, the participants in this study reported drinking approximately 2 glasses of milk per day, which equals an estimated 600 mg of calcium per day. Based on this data, we have to reconsider the amount of calcium intake among pregnant Thai women. As such and in other words, pregnant Thai women in this study may not be classified as a low calcium intake population. More to the point, calcium supplementation among participants in this study may not have yielded the high benefits reported in low calcium intake settings, because they have a higher daily calcium intake from food than previously thought. It should also be noted that the calcium intake characteristics among participants in this study may not be generalizable to pregnant women across Thailand. Further studies should be conducted to more precisely evaluate the daily dietary calcium intake in pregnant Thai women, as compared to intake among non-pregnant Thai women.

Conclusion

No risk reduction effects were observed for either hypertensive disorder in pregnancy or for delivering small for gestational age infants. More than half of all calcium supplementation participants experienced side effects from calcium supplementation treatment. Almost half of the treatment group patients experienced constipation, with others reporting bloating and nausea.

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Conflict of interest

None of the authors has any potential conflict of interest to disclose.

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