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Calcium supplementation to reduce blood lead levels in pregnant women (Studies in the northern coastal region Brebes, Indonesia)

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Abstract

Background: Lead exposure during pregnancy can inhibit fetal growth and increase the risk of gestational hypertension even preeclampsia. Calcium supplementation may inhibit the lead absorption and mobilization of maternal bone lead. **Objective:** This study aims to evaluate the effect of calcium supplementation on reducing blood lead levels (BLL) in pregnant women. **Materials and Methods:** Quasi-experimental study with 26 pregnant women as the intervention group and 27 pregnant women as the control group was determined based on the region (cluster randomization). Supplementation of 2x500 milligram calcium carbonate tablets was given for 45 days. BLL were measured using atomic absorption spectrophotometry (AAS) and carried out before and after the intervention. Data analysis used independent t-test, Mann-Whitney test, and Wilcoxon test. **Results:** There was no significant difference in age, gestational age, and blood calcium levels between the treatment and control groups. The mean BLL pre-test of the intervention and control groups were in the high category (34.7±21.99 vs 26.8±15.50 µg/dL). There was a significant difference in the reduction in blood lead levels between the intervention and control groups ($p = 0.001$). In the intervention group, there was a decrease in BLL by 6.5 µg/dL, while in the control group, there was an increase of 2.9 µg/dL. **Conclusions:** Calcium supplementation can reduce blood lead levels in pregnant women.

Keywords: calcium, lead, pregnant, quasi-experimental, supplementation

Key Messages:

Lead exposure to pregnant women causes health problems for both mother and child, such as the occurrence of preeclampsia (PE), stunting, deficit in central nervous system functioning, and attention

deficit hyperactivity disorder (ADHD). Calcium supplementation 2x500 mg can reduce blood lead levels in pregnant women.

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Introduction

The quality of human resources in the future is determined from the start of pregnancy (conception) until the child is two years of age. This stage is commonly referred to as the first thousand days of life (the first 1,000 days). A balanced intake of nutrients is needed in order to achieve optimal individual growth. Apart from nutritional intake, healthy environmental conditions can also affect the growth and development process. Exposure to toxic substances in the environment, such as lead¹ and/or pesticides², before and during pregnancy can cause serious pregnancy complications, namely high blood pressure or gestational hypertension (GH), which directly affects the condition of the fetus/baby at the first 1,000 days, such as the occurrence of low birth weight and preterm delivery.³ Hypertensive disorders of pregnancy, a general term covering gestational hypertension, preeclampsia (PE), and eclampsia, are a significant cause of maternal and perinatal morbidity and mortality.⁴

The cause (etiology) of GH and PE is still uncertain, but one theory relates to the occurrence of oxidative stress during pregnancy.⁵ Exposure to toxic substances in the environment, such as pesticides² and lead (plumbum, Pb)⁶ can trigger oxidative stress and cause an increase in blood pressure.¹ Several studies have also shown that lead exposure has the potential to increase the risk of hypertension⁷ and even pre-eclampsia in pregnant women.⁸

Calcium is the most abundant mineral in the body and is important for many diverse, including bone formation, muscle contraction, and enzyme and hormone function. Most of the body's calcium is found in bones and teeth. Inadequate calcium consumption by pregnant women can cause adverse effects on both the mother and the fetus, including delayed fetal growth, low birth weight, and poor fetal mineralization.⁹ Calcium requirements increase during pregnancy to meet the developing fetus's needs for bone mineralization and growth.¹⁰

Lead and calcium compete for the same location in the body and are stored in the bones. During pregnancy, lead is released from the bones by resorption (recycling of calcium and other minerals including lead from the bones into the bloodstream).¹¹ Several studies have shown that calcium supplementation can reduce blood lead levels.^{12,13}

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Materials and Methods

Design and study population. This study used a quasi-experimental design. The research was conducted in four Primary Health Care (PHC) in Brebes district, namely Wanasari, Bulakamba, Kluwut, and Tanjung. Determining into the intervention or control groups was carried out non-randomized, but based on the region (cluster randomization), for the convenience and practicality of monitoring the compliance of subjects taking calcium tablets. Pregnant women from Wanasari and Bulakamba ($n=38$) became the control group and those from Kluwut and Tanjung became the intervention group ($n=40$). At the end of the study, there were 26 subjects in the intervention group (65.0%) and 27 subjects in the control group (71.1%) who were successfully followed up (can be taken blood lead levels of data post-test).

The intervention group received additional 2x500 milligram calcium carbonate tablets given for 45 days, in addition to the calcium tablets given by the Primary Health Care (PHC) in accordance with the PHC routine program for pregnant women, while the control group only received calcium tablets from the PHC routine program. Monitoring adherence to taking calcium tablets was carried out through home visits every two weeks.

Laboratory test. Blood lead levels were measured using atomic absorption spectrophotometry (AAS). As much as 5 cc of venous blood was taken by a competent health analyst, then checked for blood lead levels at the GAKY laboratory, Universitas Diponegoro, Indonesia. Blood lead levels were measured before and after the intervention. Blood calcium levels were measured before the intervention using 5-nitro-5'-methyl-BAPTA(NM-BAPTA).

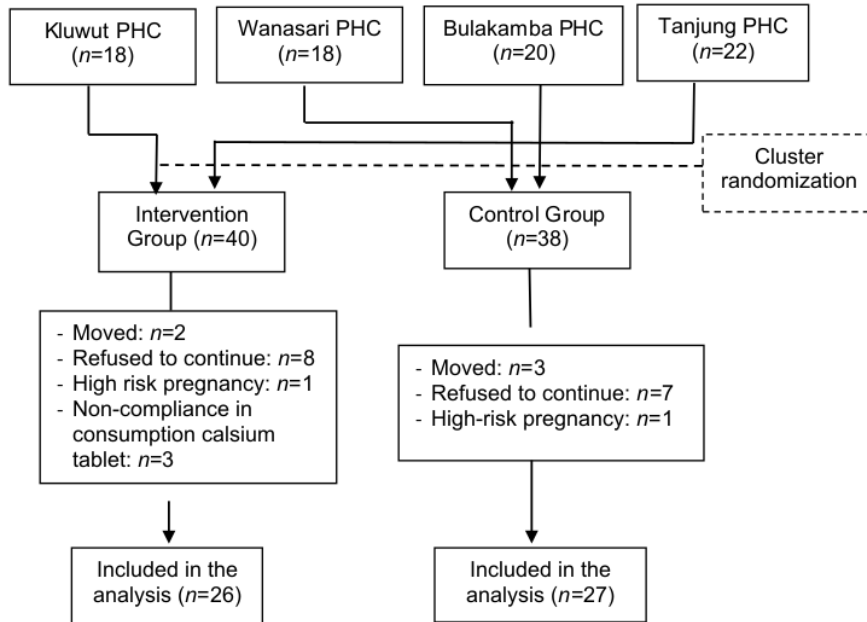
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Statistical analysis. Comparison of the baseline characteristics of subjects between the intervention and control groups using the Mann Whitney test and independent t-test. Comparison of blood lead levels pre-test, post-test, and pre-post changes, between the treatment and control groups using the Mann Whitney test and independent t-test. Statistical analysis was performed by IBM SPSS statistic 20.

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Ethics. The study protocol was approved by the Ethics Committee on Health Research, Faculty of Public Health, Universitas Diponegoro, Semarang, Indonesia (178/EA/KEPK-FKM/2018). All participants or their guardians gave written informed consent.

Results

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At the beginning of the study, there were 40 subjects as the intervention group and 38 subjects as the control group. In the course of the study for two months, 26 subjects in the intervention, and 27 subjects in the control group were obtained whose data were complete and analyzed (Figure 1).

Figure 1: Study sample profile



The results showed that there was no significant difference in age, gestational age, and blood calcium levels between the treatment and control groups. (Table 1)

Table 1: Comparison of subject characteristics between intervention and control groups

Characteristics	Group (mean±SD; median; min-max)		p
	Intervention (n=26)	Control (n=27)	
• Age (years)	27.4±4.41; 27.0; 20-35	28.8±4.30; 28.0; 21-35	0.155 ^a
• Gestational age (weeks)	23.3±8.22; 25.5; 8-32	20.7±6.10; 20.0; 9-32	0.167 ^b
• Blood Ca levels(mg/dL)	8.5±0.43; 8.5; 7.9-9.8	8.6±0.30; 8.6; 8.1-9.1	0.455 ^b

^a Mann-Whitney independent-test

The results before intervention showed that the mean blood lead levels (BLL) of the intervention and control groups were in the high category (34.7±21.99 vs 26.8±15.50 µg/dL). The mean BLL in the treatment group and the control group were not significantly different (p = 0.393). BLL after treatment in the treatment group showed a mean decrease; on the other hand, the control group tends to increase. The results of the Mann-Whitney test proved that there was no difference in BLL after treatment between the two groups (p = 0.702). The results of the independent t-test showed a

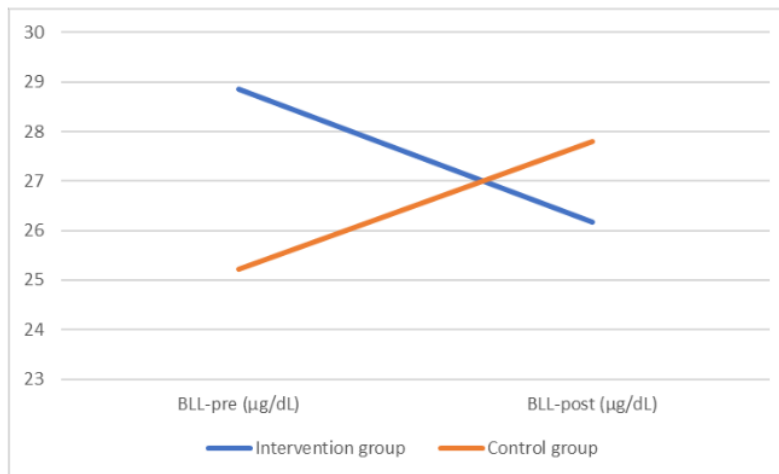
significant difference in the mean change in BLL between the intervention and control groups ($p = 0.001$) (Table 2). Figure 2 showed a tendency to decrease BLL in the intervention group, meanwhile, it tends to increase in the control group.

Table2: Comparison of pre-test, post-test and change (pre-post) BLL between treatment and control groups

Blood Lead Levels ($\mu\text{g/dL}$)	Groups (mean \pm SD; median; min-max)		p
	Intervention (n=26)	Control (n=27)	
• Pre-test	34.7 \pm 21.99; 25.5; 9-71	26.8 \pm 15.50; 23.0; 6-72	0.393 ^a
• Post-test	28.2 \pm 15.53; 28.5; 6-60	29.6 \pm 13.57; 28.0; 12-64	0.702 ^a
• Change (pre-post)	6.5 \pm 12.23; 5.0; -16.0-36.0	-2.9 \pm 5.11; -3.0; -15.0-8.0	0.001 ^b

^aMann-Whitney independent-test

Figure 2: The differences in BLL changes in the intervention and control groups



Discussion

Our study showed that calcium supplementation of 2x500 mg for 45 days can reduce BLL in pregnant women. The mean reduction in blood lead in the intervention group reached 6.5 $\mu\text{g/dL}$, while the control group tended to increase with an average of 2.9 $\mu\text{g/dL}$ ($p=0.001$). This result is consistent with the results of a study by Ettinger et al. (2009) of the effects of calcium supplementation on BLL in pregnancy. The authors found that calcium supplementation was associated with a modest reduction in blood lead when administered during pregnancy and may constitute an important secondary prevention effort to reduce circulating maternal lead and, consequently, fetal exposure.¹³

During pregnancy, the need for calcium increases, especially for fetal growth.^{10,14} Calcium consumption is essential for bone development and maintenance throughout life, especially crucial during pregnancy and lactation. There is concern that if calcium in the diet is insufficient to meet this extra demand, the health of the mother and baby may be compromised because of bone loss from the maternal skeleton, reduced fetal growth and bone mineralization, and impaired breast-milk calcium secretion.^{10,15}

Lead, like calcium, is stored in bones and generally does not circulate throughout the body. But the demands of pregnancy and lactation trigger the release of calcium, which also release lead into the maternal bloodstream.¹⁶ Several studies showed the effects of lead exposure to maternal health, such as the occurrence of preeclampsia (PE)^{17,18} and the health of children, especially related to growth and development, such as stunting¹⁹, the deficit in a central nervous system functioning²⁰, and attention deficit hyperactivity disorder (ADHD).^{21,22} Data from Brebes District Health Office showed approximately 40% of maternal deaths in this location due to PE, and there may be a role of lead exposure.

Calcium supplementation can reduce bone resorption and consequent mobilization of maternal bone lead decreases. A case-crossover trial study of calcium supplementation during the third trimester of pregnancy showed that maternal bone resorption, as reflected by urinary cross-linked N-telopeptide, was reduced by an average of 13.6 nM bone collagen equivalents/mM creatinine (14%) compared with placebo. This result indicated that calcium supplementation can suppress maternal bone mobilization.^{23,24} Calcium may also reduce the absorption of lead in the gastrointestinal tract and/or increasing the excretion of lead from circulation.^{25,26}

Although calcium supplementation has a positive effect on reducing BLL, calcium intake from food still plays an important role in suppressing the mobilization of lead from the maternal bones, and decreasing the absorption of lead that enters orally in the digestive tract, which will reduce the risk of fetal and infant exposure. In addition, calcium supplementation also has a positive impact in reducing the risk of gestational hypertension/PE, which is one of the main causes of maternal mortality.²⁷

Related to the causality, there was a limitation in this study, there was no randomization in subjects grouping. The cluster-randomized method used in this study has a diminishing return in power and precision as cluster size increases²⁸, but the relatively similar subjects' characteristics in the two groups prove that their potential as confounders can be controlled. Geographical conditions are relatively similar between intervention and control areas, most of the coastal areas and onions agricultural so that the socio-economic conditions of the two groups are also not different.

Finally, it is concluded that calcium supplementation 2x500 mg in the northern coastal region can reduce BLL in pregnant women. The calcium supplementation program for pregnant women in the

study area needs to be prioritized in order to prevent the negative effects of lead exposure, reduce the incidence of PE and fetal growth disorders, and even reduce maternal mortality in the long term.

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