



Calcium supplementation on lowering blood pressure in pregnant women with hypertension: A meta-analysis

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ABSTRAK

Latar Belakang : Hipertensi dalam kehamilan menyebabkan 10% gangguan kehamilan di seluruh dunia yang berakibat pada morbiditas dan mortalitas pada ibu sebesar 9-26% dan kejadian kelahiran premature sebanyak 15% di seluruh dunia. Dari hasil metaanalisis sebelumnya, ada hubungan asupan kalsium dengan kejadian preeklampsia dengan mengkonsumsi kalsium 1500-2000mg selama kehamilan diperlukan penambahan suplemen kalsium pada ibu hamil karena tidak semua asupan kalsium pada ibu hamil dari pangan cukup untuk memenuhi kebutuhan kalsium.

Tujuan : Menganalisis studi penelitian tentang pengaruh kalsium terhadap tekanan darah sistolik pada ibu dengan hipertensi hamil dalam kehamilan, Menganalisis studi penelitian tentang pengaruh kalsium terhadap tekanan darah diastolik pada ibu hamil dengan hipertensi dalam kehamilan

Metode : Meta analisis dengan mencari 24 studi penelitian dari 5 database (Pubmed, Science Direct, Google Scholar, Elsevier, dan Proquest) dengan menggunakan Randomized Control Trial (RCT), Eksperimental, dan Kohort, yang diterbitkan tahun 2013-2020.

Hasil: hasil analysis dari 5 studi yang melibatkan 945 ibu hamil yang terpilih dengan rata-rata penggunaan dosis sedang (500 mg/hari selama penelitian) yang terbagi dalam 2 kelompok. Pemberian intervensi kalsium diberikan sejak usia kehamilan 20 minggu menunjukkan bahwa suplementasi kalsium memberikan dampak penurunan terhadap tekanan darah ibu pada hamil. Analisis menunjukkan adanya perbedaan tekanan darah pada ibu dengan hipertensi dalam kehamilan dibandingkan dengan ibu yang tidak mengkonsumsi kalsium.

Kesimpulan : Penggunaan Suplemen kalsium selama masa kehamilan dapat mengurangi tekanan darah dan mencegah terjadinya preeklampsia. Dosis yang dianjurkan adalah 500 mg/hari sejak usia kehamilan 20 minggu dengan pada ibu dengan risiko preeklamsi. Tenaga kesehatan perlu untuk memastikan bahwa ibu hamil mematuhi aturan konsumsi kalsium yang diberikan agar rekomendasi penatalaksanaan dapat dijalankan dengan baik

KATA KUNCI : hipertensi dalam kehamilan; tekanan darah sistolik; tekanan darah diastole; kalsium.

ABSTRACT

Background: Hypertension in pregnancy causes 10% of pregnancy disorders worldwide which results in maternal morbidity and mortality of 9-26% and the incidence of premature births as much as 15% worldwide. From the results of previous meta-analysis, there is a relationship between calcium intake and the incidence of preeclampsia by consuming 1500-2000mg calcium during pregnancy, it is necessary to

add calcium supplements to pregnant women because not all calcium intake in pregnant women from food is sufficient to meet calcium needs.

Objectives: *Analyzing research studies on the effect of calcium on systolic blood pressure in pregnant women with hypertension in pregnancy, Analyzing research studies on the effect of calcium on diastolic blood pressure in pregnant women with hypertension in pregnancy.*

Methods: *Meta analysis by searching 24 research studies from 5 databases (Pubmed, Science Direct, Google Scholar, Elsevier, and Proquest) using Randomized Control Trial (RCT), Experimental, and Cohort, published in 2013-2020.*

Results: *the results of the analysis of 5 studies involving 945 selected pregnant women with an average use of moderate doses (500 mg / day during the study) were divided into 2 groups. Providing calcium intervention since 20 weeks of gestation showed that calcium supplementation had a decreasing impact on maternal blood pressure in pregnancy. Analysis showed a difference in blood pressure in mothers with hypertension in pregnancy compared to mothers who did not consume calcium.*

Conclusions: *The use of calcium supplements during pregnancy can reduce blood pressure and prevent preeclampsia. The recommended dose is 500 mg/day from 20 weeks of gestation with mothers at risk of preeclampsia. Health workers need to ensure that pregnant women comply with the calcium consumption rules given so that the management recommendations can be carried out properly*

KEYWORD: *hypertension in pregnancy; systolic blood pressure; diastolic blood pressure; calcium.*

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INTRODUCTION

Hypertension complicates approximately 3-10% of all pregnancies and 11% of first pregnancies, half of which are associated with preeclampsia, and causes up to 30,000 maternal deaths worldwide each year. Preeclampsia is defined as high blood pressure and proteinuria occurring after the twentieth week of pregnancy (1). In 2019, the maternal mortality in Indonesia remained high at 305 per 100,000 live births, which is still far from the Sustainable Development Goals (SDGs) target of 70 per 100,000 live births by 2030 (2). Uncontrolled hypertension will progress to the level of preeclampsia and has a 40% risk of eclampsia (3,4). Calcium is a mineral that participates in several important functions. Although research on the role of

calcium has focused mainly on bone health, the effects of calcium or calcium supplements have recently focused on other health effects (5).

Calcium levels in the blood play an important role in helping the contraction of blood vessel wall muscles and signaling the release of hormones that play a role in blood pressure regulation. The average calcium intake of Indonesians is 254 mg/day in Indonesia (6). During pregnancy, to maintain a positive balance, it is recommended to increase the amount of calcium by 1300 mg/day, according to other guidelines metabolic adjustments compensate for the calcium needs required during pregnancy. Since 2013, WHO has recommended that all

pregnant women with low calcium levels receive calcium supplements of 1500-2000 mg/day at 20 weeks of gestation, as the results of randomized controlled trials show a reduced risk of preeclampsia (5).

Results showed that calcium supplementation of at least 1 g daily starting around mid-pregnancy was associated with a moderate reduction in pre-eclampsia, and particularly reduced the occurrence of severe pre-eclampsia, especially in women at high risk, or with low dietary calcium intake. Reviews of low-dose calcium supplementation (500 mg/day at 20 weeks' gestation), with or without other supplements, including small trials of variable quality, also found a reduction in pre-eclampsia (1).

Research on hypertensive pregnant women by giving calcium-composed milk with an intake of 400mg obtained from 26 respondents, 16 respondents (61.5%) experienced a decrease in blood pressure (BP) and 10 respondents (38.5%) remained hypertensive. Statistical analysis showed a relationship between calcium administration and blood pressure in hypertensive pregnant women (7).

The study by Sun et al involved 27 studies, with 28,492 pregnant women included. The results showed that giving calcium can reduce the incidence of preeclampsia (RR 0.51, 95% CI: 0.40 to 0.64) and in gestational hypertension (RR 0.70, 95% CI: 0.60 to 0.82). Giving calcium supplements at high doses (1.2-2 g/day), moderate doses (0.6-1.2 g/day), and low doses (<0.6 g/day) can reduce the risk of preeclampsia. reduction in the risk of gestational hypertension occurred at high doses and moderate doses (8). Another study mentioned that the administration of

high doses of calcium (1.5g - 2g) was effective in preventing preeclampsia, but there was no difference in the effectiveness between the administration of high doses of calcium and the administration of low doses of calcium on the incidence of preeclampsia (9)

In previous studies, calcium administration in pregnant women was about 10.25%, namely 100mg / day. However, these results had no effect on increasing calcium in pregnant women. Another study on calcium content in food is in moringa leaves 440 mg / day and cow's milk 140 mg / day obtained the results of moringa leaves respectively 0.518%, 0.522% and 0.447%, while in fresh cow's milk, respectively 0.090%, 0.081%, and 0.086%. So that the average obtained in moringa leaves is 0.505% and fresh cow's milk is 0.085%, the difference between the two samples is 0.42%. Calcium obtained in moringa leaves contains 17 times more than fresh cow's milk (10).

Management of hypertension during pregnancy depends on blood pressure level, gestational age, and the presence of relevant maternal and fetal risk factors. However, almost all drugs recommended in recent international guidelines have questionable fetal safety profiles (11, 12). Nonpharmacologic therapies have always been considered unimportant in the management of hypertension during pregnancy, but the role of calcium should be considered in the light of recent evidence. There are a number of randomized clinical trials testing the efficacy and safety of dietary supplements during pregnancy, with encouraging results (13). In addition, prevention of pre-eclampsia can be done by handling predictions and early detection in risk

groups (14) as well as ensuring that pregnant women can meet their mineral and nutritional needs which play a role as one of the predictive etiologies of hypertension in pregnancy(15).

This article aims to analyze the effect of calcium supplementation on blood pressure based on several studies that have been conducted on pregnant women with hypertension in pregnancy.

MATERIALS AND METHODS

Researchers conducted article searches through accessible journal databases such as Pubmed, MEDLINE, Proquest, Google Scholar, ACM digital library, SCOPUS, and Science Direct using the PRISMA method.

Article search results using selected keywords with the addition of : "Calcium" and "Hypertension" or "blood pressure" and "pregnant women" or "pregnancy", "Calcium supplement" and "blood pressure" and "pregnant woman", "Calcium supplement and blood pressure pre-eclampsia", "Calcium and Vit D and blood pressure hypertention pregnancy", "Calcium and Vit D" and "blood pressure" and "preeclampsia". The researched topics accessed in this research process were filtered based on the following criteria:

1. Journals published within a 10-year time span (2011-2021)
2. Article type with Randomized Control Trial design
3. Articles using Indonesian and English
4. Articles can be accessed in full/available full text

Meta-analysis is analyzed through five steps as follows: a.

1. Formulate the research question in PICO format (Population, Intervention,

Comparison, Outcome).

2. Search for primary study articles from a wide variety of electronic databases including Google Scholar, SpringerLink, Pub Med, and Non-electronic databases.
3. Screen and critically appraise the primary study articles.
4. Performed extraction and synthesis of effects data using RevMan 5.4.
5. Interpret and summarize the results.

Inclusion Criteria: Time period of the research article Journal publication time span is maximum 10 years. Time of article publication between 2011-2021. Language using Indonesian and English The research subject is pregnant women. Original journal type is RCT article. Intervention is using Calcium. The outcome measure used is blood pressure.

Exclusion Criteria:

1. Exclusion criteria in this study include:
2. Articles that do not discuss the effect or effectiveness of calcium on blood pressure in pregnant women.
3. Respondents with comorbidities such as: hypertension, renal failure, There are maternal and fetal health disorders
4. Subjects who are not pregnant women
5. Articles do not have full text / non full text
6. Research other than original research such as reviews, editorials, and others .

Study Instruments: Articles that analyze the correlation between calcium supplementation and blood pressure reduction in pregnant women. This study was conducted using a checklist for critical review of cross sectional studies (surveys), calcium tablets and blood pressure meters.

Data analysis: The collected studies were screened using the specified criteria, next were the studies' results analyzed based on

the variation between studies with fixed effect model and random effect model by using revMan 5.3 software issued by Cochrane collaboration. RevMan software serves to calculate the overall OR value by explaining the 95% Confidence Interval (CI) using the effect model and heterogeneity of the data.

RESULTS AND DISCUSSION

RESULTS

Based on the results of literature search through publications in the database and using calcium keywords. Keywords for article searches are combined using the Boolean Operators (AND) system. Researchers obtained 1086 articles that match the keywords. The search results that

have been obtained are then checked for duplication, found that there are 674 articles that are the same so they are excluded and 439 articles remain. Researchers then screened based on titles that were adjusted to the theme, 439 articles were excluded because they were not suitable and 49 articles remained. Then the researcher continued again based on full text screening, so that 390 articles were discarded because the article did not meet the inclusion criteria such as study design, population, outcome and type of intervention. This left 24 articles that could be used in the Meta-analysis. The results of the selection of study articles can be depicted in the Flow Diagram below:

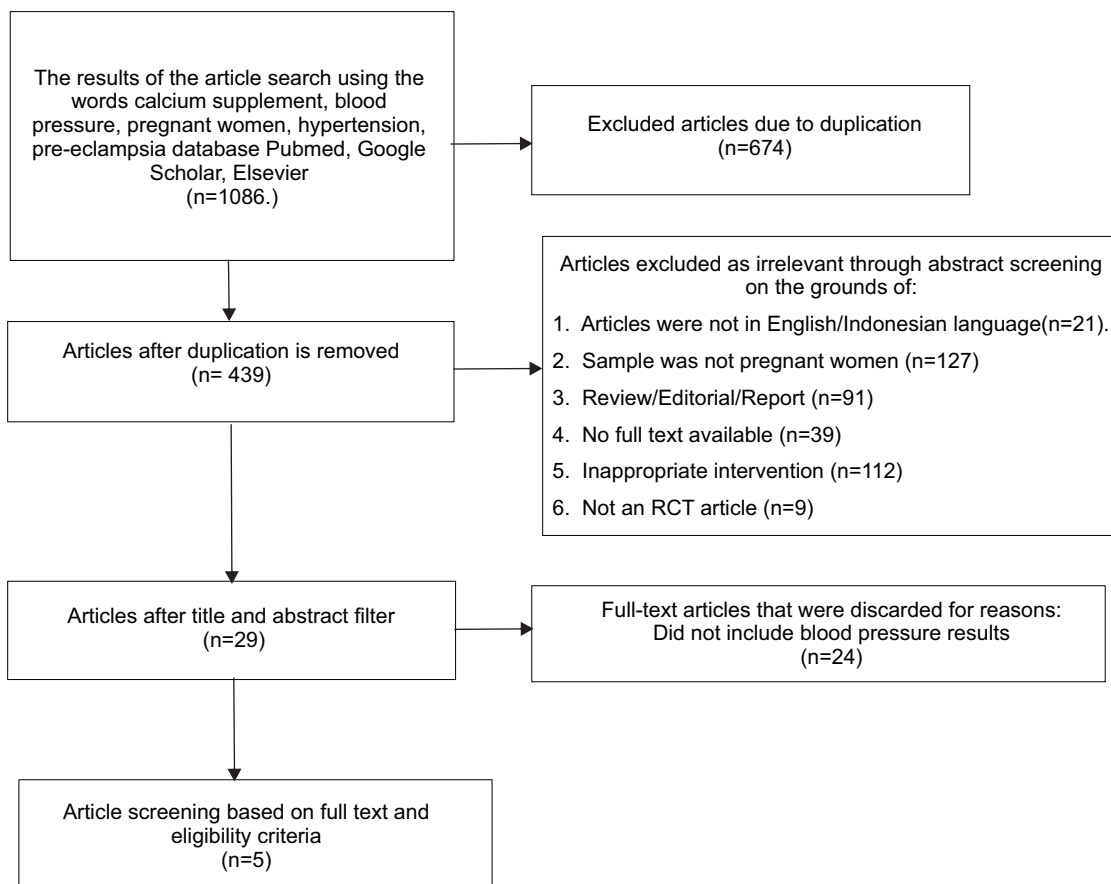


Figure 1. Screening flow diagram

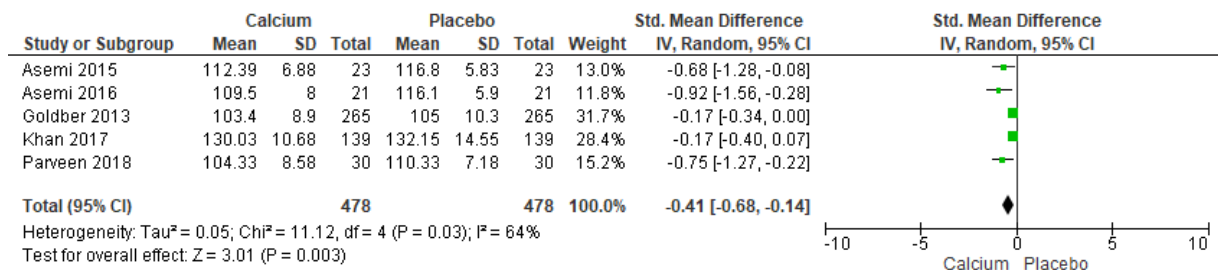


Figure 2. Flow diagram of calcium intervention

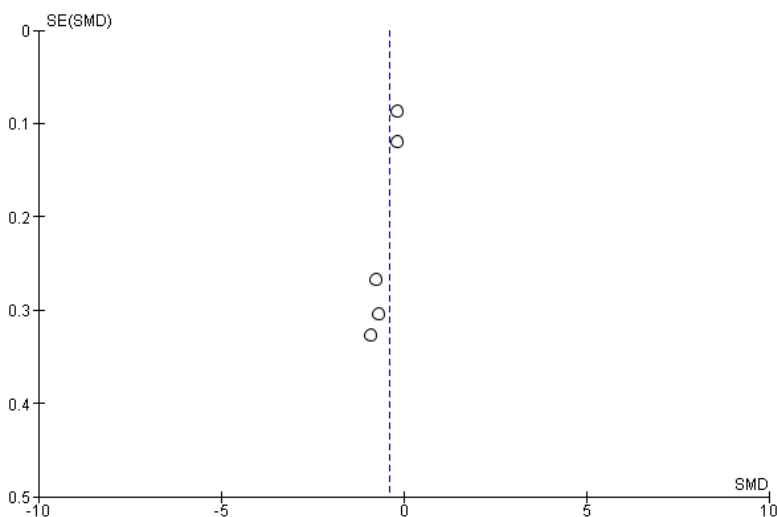


Figure 3. Forest plot

Figure 3 shows that the distribution of the effect estimates is more likely to be to the left of the vertical line of the average effect estimate than to the right. Hence, this funnel plot indicates the presence of publication bias. Since the distribution of these effect estimates is located in the left hemisphere of the mean vertical line, which is in the opposite direction to the diamond shape in the forest plot image, the publication bias is more likely to increase the effect of calcium administration on the risk of hypertension in pregnant women (underestimate).

DISCUSSION

During pregnancy, increased calcium absorption occurs and is stimulated by several hormones (vitamin D, estrogen, lactogen, and prolactin) and shows higher retention in the renal tubules. Intestinal Calcium (Ca) absorption is divided into two parts: active,

which is mediated by vitamin D and involves Ca-binding proteins (Ca-Bp), and passive, which can relate to direct or facilitated (carrier-mediated) diffusion(16). The use of calcium in pregnancy hypertension is essential, as a lack of calcium in the diet can lead to hypertension. Calcium plays a role in maintaining the concentration in the blood during muscle contraction. Muscle contraction in blood vessels is very important because it can maintain blood pressure.

Lack of calcium intake can increase high blood pressure because it stimulates the release of parathyroid hormone and/or renin, which leads to an increase in calcium concentration within vascular smooth muscle cells and causes vasoconstriction. Calcium supplements may help reduce the risk of hypertension in pregnancy by reducing parathyroid calcium release and intracellular calcium concentration, resulting in decreased

Table 1. Critical Appraisal Assessment

Assessment Item	Publications				
	Asemi (2015)	Asemi (2016)	Goldber (2013)	Khan (2017)	Parveen (2018)
Relevance of objectives and problem	1	1	1	1	1
Relevance of the method and problem	1	1	1	1	1
Sufficient samples	1	1	1	1	1
Validation of samples	1	1	1	1	1
Comparable Cases and Controls	1	1	1	1	1
No bias	1	0	1	1	1
Information data tracking	1	1	1	1	1
Analysis of relevant and valid data	1	1	1	1	1
Relevance Effect Size	1	1	1	1	1
Reporting 95% CI	1	1	1	1	1
Reported confounding factors	1	1	1	0	1
Results can be applied	1	1	1	1	1
Total	12	11	12	11	12

smooth muscle contraction and increased vasodilation(15). Supplemental calcium during pregnancy has been shown to be effective in reducing the risk of pre-eclampsia in pregnant women who are having their first pregnancy(17).

The use of calcium supplements has an important role in reducing the problem of hypertension during pregnancy. This can be achieved by decreasing the release of parathyroid calcium and the concentration of calcium in the cells, so that smooth muscles become more relaxed and blood vessels become more dilated. By following the rules of taking calcium supplements regularly, pregnant women with preeclampsia can lower their blood pressure.

The results of research conducted by Anita of case study, low calcium levels in pregnant women showed a statistically significant relationship to the incidence of

preeclampsia (OR 3.4, 95% CI 1.092 -10.723) (18). Supplemental calcium during pregnancy has a significant association with a reduced risk of developing preeclampsia. Ten RCT studies have included a total of 11,405 women, of which 5,697 women were in the intervention group and 5,708 were in the control group. The results showed a 59% reduction in the risk of preeclampsia (RR 0.41; CI 0.24-0.69) in developing countries. However, calcium supplementation had no significant effect in developed countries. According to the Food and Drug Administration (FDA), the benefits of calcium supplementation cannot be generalized to developed countries due to differences in low baseline calcium intake in developing countries (<900 mg/day)(19).

Supplementing in mid-pregnancy may reduce the serious problems caused by preeclampsia, but it does not solve all the problems caused by the condition. Therefore,

Tabel 2. PICO Screening

Researcher	P (Population)	I (Intervention)	C (Comparison)	O (Outcome)
Asemi (2015)	46 Pregnant women at risk of pre-eclampsia. 25 weeks Gestation 27 weeks gestation (23 intervention; 23 control)	Calcium 800 mg Magnesium 200 mg Zinc 8 mg Vit. D3 400 IU For 9 weeks	Placebo For 9 weeks	Multi mineral group+ Vit. D SBP: 113.47±4.86 decreased to 112.39±6.88 (mean decrease -1.08, p =0.34) DBP: 66.30±6.43 decreased to 65.86±7.17 (mean decrease -0.44)p =0.70 Placebo group SBP: 110.00±6.03 increased to 116.08±5.83 (mean difference 6.08 with p =0.001) DBP: 66.95±5.38 increased to 70.00±5.83 (mean difference 3.05, with p = 0.007)
Asemi (2016)	Study subjects 42 healthy pregnant womens Aged 18-40 years 25 weeks gestational 21 control, 21 intervention	Calcium Carbonate 500 mg+200Iu Vit.D/day for 9 weeks	Placebo for 9 weeks	Intervention Systole 106.9±5.3 increased to 109.5±8.0 (difference 2.6±8.7) Control 109.5±5.9 increased to 116.1±5.9 p value = 0.11 Diastole Intervention: 65.7±5.0 to 63.8±5.5 (decrease 1.9±3.3) Placebo and diastole 66.7±5.5 to 69.8±6.0 (increase 3.1±5.2) p value = 0.02
Goldber (2013)	Results 525 pregnant women (260 intervention; 265 control) Pregnant women from 20 weeks' gestation to delivery with primary examination at 36 weeks' gestation.	Intervention: 3x500/day Chewable calcium carbonate tablets.	Control: 3x500mg placebo tablets (Cellulose+Lactose) from 20 weeks gestation to delivery)	Calcium administration showed no significant difference (p =0.8) Calcium: SBP: 101.2±9.0 increased to 103.4±8.9 (mean: 2.2mmHg) DBP: 54.5±7.3, increased to 58.4±8.2 (mean: + 4.0mmHg) Placebo: SBP: 102.1±9.3, increased to 105.0±10.3 (mean: + 2.8 mmHg) DBP: 55.8±7.8 increased to 59.6±9.3 (mean: + 3.8mmHg)
Khan (2017)	Study subjects were 272 nulliparas; (123 intervention; 139 control) Pregnant women with BP <140/90 mmHg and	Intervention: 2 gr/hr (4 500 mg tablets); Started at 20 weeks gestation until delivery	Control: 500 mg/hr. (4 Tablets =1 Ca tablet, 3 Placebo)	Mean SBP: Intervention Group: 130.03 ± 10.68 Control Group: 132.15 ± 14.55 (p=0.0001) Mean DBP: Intervention Group: 81.44 ± 8.65

future studies should be conducted to evaluate calcium supplementation earlier in pregnancy. Giving low doses of calcium in early pregnancy may also reduce the risk of pathology in pregnant women. The rationale for early calcium supplementation is based on the theory that placenta formation and development lasts until the middle half of pregnancy(20).

One hundred and forty-eight patients were involved in the study on calcium supplementation in the prevention of preeclampsia. The average age of the patients was 27.2±6.01 years. From the results of the study Calcium supplementation was found to

be effective in preventing preeclampsia in 79.05% of high-risk women. supplemental calcium may reduce systolic and diastolic blood pressure and prevent preeclampsia. Although recommended for pregnant women at risk of preeclampsia, calcium supplements may provide the same benefits to all pregnant women.(21)

An assessment of calcium consumption during pregnancy showed an average difference in calcium consumption of about 400-500 mg/day between low-income and high-income countries. WHO guidelines recommend calcium supplementation of 1.5 to 2 g/day for pregnant women from populations

with low baseline consumption; however, more recent evaluations suggest that supplementation with 500 mg/day of calcium during pregnancy has the same effect as supplementation with higher doses.

On the other side, dietary calcium supplement compliance is still lacking. This is due to several factors such as nausea after taking calcium supplements, often forgetting to take, unpleasant smell, and feeling healthy and not needing supplements. Another study also stated that problems such as nausea, vomiting, and busyness are obstacles for pregnant women to comply with the recommended supplement consumption(22). Therefore, health workers need to remind mothers to consume calcium in accordance with the dose and combined with vegetables that can help the absorption of calcium.

CONCLUSION AND RECOMMENDATION

Based on the previous discussion, the results showed the use of calcium supplements during pregnancy may reduce blood pressure and prevent preeclampsia. The use of calcium supplements is recommended for pregnant women at risk of preeclampsia, but more data is needed on the effects of calcium on maternal and fetal health.

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