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# Does Supplementation with Vitamin D and Calcium Reduce the Risk of Developing Pre-eclampsia Compared with Prophylactic Daily Aspirin Use?

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## Abstract

– Pre-eclampsia is a hypertensive disorder that occurs during pregnancy. Onset is typically around the 20 week of gestation and serious complications may occur if it is not properly managed. Complications from pre-eclampsia include preterm delivery, disease progression to eclampsia, organ damage, placental abruption, and neonatal complications. Initial management involves the use of antihypertensive medications. Current guidelines recommend the initiation of 81 mg aspirin starting at 12 weeks gestation for women with increased risk factors. The goal of this literature review is to examine the effectiveness of calcium and vitamin D supplementation compared to daily prophylactic aspirin use for prevention of pre-eclampsia. The databases utilized for this literature review include Pub-Med, Cochrane Library, Clinical Key, and Google Scholar. Additional relevant studies were found in reference lists of the included studies. This comprehensive review will discuss initiation of therapy, dosing, and pregnancy outcomes. Review of the literature showed a decrease in blood pressure with the use of calcium and vitamin D supplementation. However, there was a greater impact shown with calcium supplementation in populations with a dietary deficiency than those without a dietary deficiency in calcium. The effect of 150 mg daily prophylactic aspirin was shown to reduce the occurrence of preterm pre-eclampsia but did not impact pre-eclampsia after 37 weeks of gestation.

– ***Keywords*:** pre-eclampsia, aspirin, calcium supplementation, vitamin D supplementation, blood pressure, hypertensive disorders, pregnancy

## Introduction

- Pre-eclampsia is a serious hypertensive disorder that develops after the 20th week of gestation and is accompanied by proteinuria.
- Pre-eclampsia can affect many organs including the kidneys, liver, heart, eyes, and could lead to a stroke or other brain injuries.
- Medications are used to manage blood pressure in an effort to delay delivery until the baby is more mature. The protocol for medication initiation, dosage, and screening methods vary by country.
- ACOG recommends prophylactic aspirin for women with a history of pre-eclampsia.
- This study will examine if supplementation with calcium and/or vitamin D is more effective in reducing the risk of developing pre-eclampsia compared to aspirin.

## Statement of the Problem

- Pre-eclampsia may affect 3-5% of pregnant women and is a major cause of maternal and fetal complications (Fox et al., 2019).
- Delivery is the definitive treatment once pre-eclampsia develops.
- Aspirin's major effect is on cyclooxygenase which inhibits thromboxane A2 production. This inhibition balances thromboxane and prostaglandin leading to vasodilation that helps improve placental function.
- High calcium intake can be associated with an elevated serum calcium level and can lower parathyroid hormone concentrations, leading to a reduction of renal calcium absorption. This leads to increased calcium excretion which helped lowered blood pressure and decrease the risk of hypertensive disorders in pregnancy (Belizán et al., 1991).

## Research Question

– Does supplementation with Vitamin D and Calcium reduce the risk of developing pre-eclampsia compared with prophylactic daily aspirin use?

## Literature Review

**•Variability in outcomes of calcium supplementation**

•Belizán et al., 1991 suggests that alterations in hormonal regulation of calcium metabolism could decrease the incidence of some hypertensive disorders such as pre-eclampsia with considerable evidence of the association between pre-eclampsia and the changes in calcium metabolism. For systolic blood pressure there was a significant interaction between the time and treatment ($p$=0.006) but there was not a significant interaction between time and treatment for diastolic blood pressure.
•Villar et al., 2006 showed reduction in severe gestational hypertension was found to be statistically significant (RR 0.71; 95% CI, 0.61 to 0.82). Severe pre-eclampsia complications were also significantly reduced (RR, 0.76; 95% CI, 0.66 to 0.89).

**•Optimal calcium and Vitamin D supplementation dosing**

•Asemi et al., 2016 treatment groups supplements contained 500 mg calcium carbonate and 200 IU vitamin D3. The authors concluded that calcium and vitamin D play a role in regulation of the renin-angiotensin system. They may alter cellular concentrations of sodium and calcium leading to a reduction in blood pressure measurements. The calcium and vitamin D supplementation resulted in a significant reduction of diastolic blood pressure (-1.9 ± 8.3 vs. 3.1 ± 5.2 mm Hg, $p$= 0.02), but there was not a significant reduction in systolic blood pressure.
•Gernand et al., 2017 found that women with a history of pre-eclampsia had lower concentrations of vitamin D (25(OH)D) at baseline compared to women with chronic hypertension. Women with a vitamin D deficiency had a greater risk for developing early-onset pre-eclampsia compared to women with a vitamin D status ≥ 75nmol/I. The best time to test vitamin D levels in pregnancy still remains unclear.

**•Effectiveness of calcium supplementation in non-pregnant women with a history of pre-eclampsia and high-risk pregnant women**

•Hofmeyr et al., 2019 did not show a large effect but is unable to rule out a small effect using calcium supplementation as an intervention and suggests a larger trial to test small to moderate effects of calcium on pre-eclampsia. However, the prevalence of pre-eclampsia was lower in the calcium group compared to the control group. Although there was a reduction in pre-eclampsia of about 20%, the difference was not significant (RR 0.80, 95% CI 0.61 to 1.06; $p$=0.121).
•Hofmeyr et al., 2015 concluded that women with a history of severe pre-eclampsia may show a greater reduction in the diastolic blood pressure than women without a history of severe pre-eclampsia. Although there were consistent reductions in blood pressure in the treatment group compared to those of the control group the only one that was statistically significant was the reduction in diastolic blood pressure of the treatment group with a history of severe pre-eclampsia. In women with a history of severe pre-eclampsia the change in systolic blood pressure between the treatment and control group at 12 weeks was not statistically significant (95% CI, -0.9 to 7.3) but the change in diastolic pressure in the treatment group is statistically significant (95% CI, 0.4-6.4; $p$=0.2, ANOVA analysis).

**•Effectiveness and dosing of daily prophylactic aspirin use in pregnant women.**

•Lin et al., 2021 found in this study, 100 mg of aspirin daily was not effective in reducing the incidence of pre-eclampsia in high-risk Chinese women. This may have been due to the number of women enrolled in the study with chronic hypertension (49.1%). A total of 152 of the 898 women developed pre-eclampsia, about 16.9%, with 16.8% in the treatment group and 17.1% in the control group (RR, 0.986; 95% CI, 0.738 to 1.317; $p$= 0.924).
•Rolnik et al., 2017 showed that preterm pre-eclampsia was significantly reduced by 150 mg aspirin daily (0.38; 95% CI 0.20 to 0.74; p= 0.004). There was a 62% reduction in preterm pre-eclampsia in the treatment group, but there was not a statistically significant reduction in pre-eclampsia at or after 37 weeks gestation.

## Discussion

- Taking 150 mg of daily prophylactic aspirin reduced preterm pre-eclampsia (Rolnik et al. 2017)
- Aspirin is ineffective as a monotherapy for pre-eclampsia prevention in women with chronic hypertension. (ACOG, 2020)
- Calcium supplementation showed a consistent decrease in blood pressure, but it was not statistically significant. (Hofmeyr et al. 2019)
- Taking 500 mg calcium carbonate and 200 IU vitamin D3 showed a significant reduction in diastolic blood pressure. (Asemi et al. 2016)
- Taking vitamin D3 was shown to reduce blood pressure more effectively than calcium supplementation alone. (Asemi et al. 2016)

https://www.healthline.com/health/pregnancy/preeclampsia-antihypertensive-medicine

## Applicability to Clinical Practice

- The most significant results were seen in women with a low dietary intake of calcium.
- Emphasizing the need for a healthy diet during pregnancy is very important to ensure patients are getting adequate nutrients, including calcium and vitamin D.
- Calcium and vitamin D supplementation alone are not currently recommended for prevention of pre-eclampsia during pregnancy.
- Current guidelines in the United States are to follow the ACOG recommendation with a daily aspirin starting around the 12th week of gestation.

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