

## Study on Prevention of Preeclampsia using Calcium Supplements in Early Pregnancy

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### Abstract

**Introduction:** As recommended by WHO, regular calcium supplementation reduces the risk of preeclampsia. Limited food intake communities at high risk of preeclampsia also benefit from calcium supplementation. Preeclampsia and hypertension diseases are a leading cause of maternal mortality. Calcium supplementation is a low-risk, affordable measure to improve maternal and newborn health. Preeclampsia has complex causes and can only be treated by delivering the placenta. Calcium supplementation prevents nearly 50% of preeclampsia cases. Preeclampsia affects 2% of pregnancies and contributes to perinatal and maternal fatalities, mostly in low- and middle-income nations.

**Aims and Objective:** To analyze the efficiency of calcium supplements in early pregnancy in preventing preeclampsia.

**Method:** This study involved 90 participants in a randomized, double-blind, placebo-controlled design to evaluate a new obstetric care intervention's efficacy and safety. Participants were assigned to either the Calcium group, receiving 1.5 g of Calcium daily after 20 weeks' gestation, or the Placebo group. Primary and secondary outcomes were assessed after a 12-week period, and compliance was measured through surveys and follow-up. Inclusion criteria included women with a history of preeclampsia or eclampsia and an interest in future pregnancies. Exclusion criteria encompassed factors such as age, existing pregnancy, use of calcium supplements, certain medical conditions, and personal choices regarding contraception and consent.

**Results:** The study found that the Placebo group had a higher rate of complications before allocation. Compliance rates were similar between the groups, indicating comparable adherence to the intervention. Pregnancy outcomes, including pregnancy loss rates and the frequencies of live births and pregnancies progressing to 20 weeks of gestation, did not significantly differ between the Calcium and Placebo groups. Preeclampsia occurrence showed no statistically significant difference between the groups. Other outcomes did not show significant changes, including gestational blood pressure, proteinuria, pregnancy loss, preeclampsia severity, preeclampsia onset, and maternal problems. However, more individuals in the Calcium group required postpartum hospitalization of 7 days or longer compared to the Placebo group. The study found no statistically significant differences between the two groups in most outcomes assessed.

**Conclusion:** The study has concluded that Calcium can significantly prevent preeclampsia in early pregnancy.

**Keywords:** Preeclampsia, Calcium, Early Pregnancy, Pregnancy.

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## Introduction

The WHO advises regular calcium supplementation to reduce the risk of preeclampsia in pregnancy. In communities with limited food intake with a high risk for preeclampsia, calcium supplementation has also been shown to be useful in preventing preeclampsia addressed in comments made by eminent obstetrics professional organizations. Preeclampsia and other hypertension diseases are the second-leading cause of maternal mortality during pregnancy. Worldwide [1]. Calcium supplementation is a low-risk, priced preventative measure that can significantly improve mother and newborn health and might be extensively used in community-based and primary-care settings [2]. Preeclampsia is a multi-systemic illness that is unique to pregnancy and is throughout pregnancy, which is characterized by proteinuria and the onset of hypertension. Eclampsia occurs when a preeclampsia patient has otherwise unexplainable convulsions or coma. Preeclampsia is thought to have a complex etiology, with maternal and foetal factors affecting risk severity [3]. Preeclampsia and eclampsia can only be treated by delivering the placenta. According to the WHO recommendations, "In populations whose calcium intake was low, taking calcium supplements as a component of antenatal care is suggested in preventing preeclampsia amongst pregnant women, especially in women at a greater risk of hypertension." According to meta-analyses of randomized clinical studies, Nearly fifty percent of preeclampsia cases were prevented by calcium supplementation. this strong recommendation is supported by evidence of intermediate quality [4].

Preeclampsia, which affects 2% to New-onset hypertension, which affects 5% of

pregnancies worldwide, symptoms in the mother, foetus, or placenta after 20 weeks of pregnancy. Preeclampsia has a significant worldwide effect, contributing to more than 500 000 perinatal and 30 000 maternal fatalities yearly, more than 90% of which occur within low- and middle-income (LMIC) nations [5]. Furthermore, preeclampsia is linked to a disproportionately high global burden of maternal close calls, foetal growth restriction, premature delivery, and newborn morbidity. While not affect the incidence of the syndrome at term (37+0 weeks of gestation), aspirin (150 mg/day) prevents 60% of premature preeclampsia in women that were identified to be from high risk of the condition via multivariable assessment at 11+0-13+6 weeks in pregnancy accounts for a minimum of 70% for preeclampsia cases [6].

Reduce any potential negative effects of Calcium upon iron absorption by using the recommendation in the guideline states that calcium and iron supplements should be given at least several hours apart starting at 20 weeks of pregnancy [7]. This advice should be heeded. Similar evidence-based therapies, such as the supplementation of pregnancy, both folic acid and iron (IFA), have, however, fallen short owing to challenges with product composition, supply channels, and demand that arise when expectations are ramped up, making it difficult to execute under normal delivery circumstances [8]. As a result, the practical accepted standards for inclusion into the present systems of prenatal care are crucial to reap the advantages of calcium & IFA supplementation [9].

According to a prior study by Hofmyer et al., using calcium supplements throughout

pregnancy significantly lowers the chance of developing preeclampsia and gestational hypertension. Compared to trials where individuals had appropriate calcium consumption [10], this impact was particularly obvious in populations with low baseline calcium consumption. Trumbo et al.'s further work demonstrated that the beneficial effects of Calcium supplementing were seen in groups whose baseline calcium consumption was insufficient and showed that positive effects could not be generalized to the USA population [11].

## Materials and Methods

### Research design

This study was conducted from April 2022 to March 2023 which used a randomized, double-blind, placebo-controlled, single-centre design with participants from the concerned hospital on 90 patients. The primary goal of the research was to determine the efficacy and safety of a new obstetric care intervention in preventing some obstetric issues. Participants and researchers were kept in the dark about whether or not they were receiving the natural treatment. Participants were randomly assigned to one of two groups to ensure an even distribution. The patients were assigned to Calcium group who received Calcium 1.5 g of daily after 20 weeks gestation or those who received a placebo, were assigned to Placebo group. Basic characteristics of the patients in each group was determined and Primary and secondary outcomes were determined after 12-week period. Compliance factors were determined by surveying the participants after 12-week weeks and during follow-up in 20<sup>th</sup> week.

### Inclusion and exclusion criteria

#### Inclusion

- Women whose most recent pregnancy was hampered by preeclampsia or eclampsia are said to be parous.

- Women who have stated an interest in having children.

#### Exclusion

- Women under the age of 18.
- Women who were already pregnant when they enrolled.
- Taking calcium supplements, women.
- Proteinuria is persistent in women with chronic hypertension.
- Women diagnosed with or show signs of urolithiasis, renal disease, or parathyroid disease.
- Women who were single and not in a sexual relationship.
- Women who have opted for permanent means of birth control, such as a hysterectomy, tubal ligation, intrauterine device, or hormone injection.
- Women who refused to sign a consent form after receiving adequate information.

#### Statistical analysis

The statistical analysis was conducted by using SPSS 25. The statistical analysis comprised “intention-to-treat analysis (ITT)” for intervention effects, baseline characteristics comparisons, “risk ratios (RR)” with 95% Cis for categorical variables, and descriptive statistics for continuous variables. Pregnancy rates and early pregnancy loss were considered. Statisticians used SPSS, and R. Two-sided significance was 5%.

#### Ethical approval

Each patient was explained about the study process, and consent was obtained from each. The Ethical Committee of the concerned hospital has approved the study process.

#### Results

The baseline characteristics of trial participants are compared in Table 1 between the Calcium and Placebo groups. Mothers in the Calcium group were significantly less likely to be under the age

of 20 than those in the Placebo group (21.5% vs 48.8%). Different groups had different mean values for maternal body mass index, height, and blood pressure. Before allocation, the Placebo group had a higher rate of health problems than the

Calcium group (80% vs 53.3%). Neither group had a significantly different rate of past obstetric difficulties or live births. At the study's outset, these variations illuminate the individuals' original make-up in meaningful ways.

**Table 1: Baseline characteristics of participants at trial entry (pre-pregnancy sample) and of the final sample (pregnancy  $\geq$ 20 weeks' gestation) according to study group**

Characteristics	Calcium n=45	Placebo n=45
Maternal age, years	7(15.5)	6(13.3)
Maternal age <20 years	7(15.5)	22(48.8)
Maternal weight, kg	8(17.7)	23(51.1)
Maternal height, cm	9(20)	25(55.5)
Body mass index, kg/m <sup>2</sup>	12(26.6)	13(28.8)
Body mass index >30 kg/m <sup>2</sup>	14(31.1)	16(35.5)
Systolic blood pressure at randomization, mm Hg	25(55.5)	23(51.1)
Diastolic blood pressure at randomization, mm Hg	21(46.6)	28(62.2)
Any health complaint at randomization	24(53.3)	36(80)
Previous severe preeclampsia	15(33.3)	18(40)
Previous eclampsia	17(37.7)	19(42.2)
Previous HELLP syndrome	19(42.2)	26(57.7)
Previous live birth	20(44.4)	21(46.6)

The compliance of the final sample of the clinical experiment is compared between the Calcium and Placebo groups in Table 2. The analysis looks at compliance rates over time, specifically at the 80% and 50% marks. According to the data, both groups showed similar levels of compliance throughout all time intervals. Calcium group compliance ranged from 22.2% to

40%, while placebo group compliance was between 35.6% and 71.1%. Risk ratios hovering around 0.98 indicated similar adherence rates to the intervention. According to these results, there was no statistically significant difference in compliance between the Calcium and Placebo groups.

**Table 2: Compliance of participants in the final sample (pregnancy  $\geq$ 20 weeks gestation)**

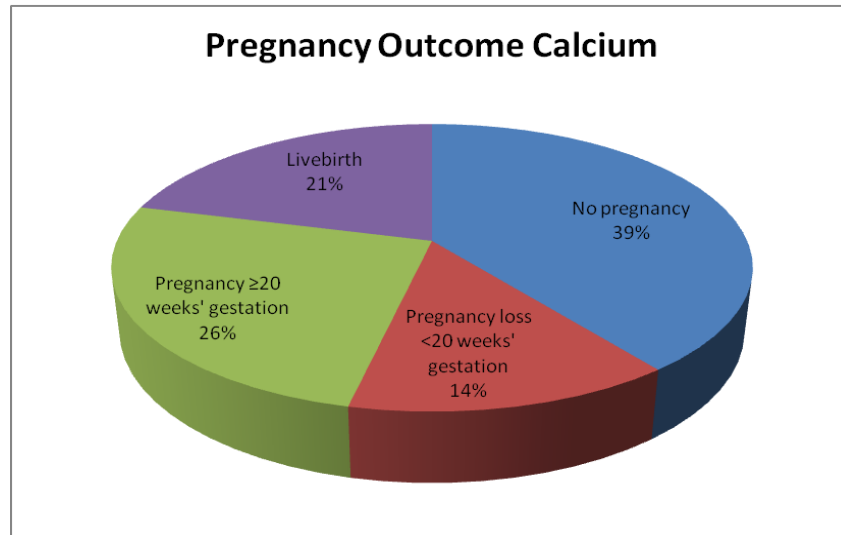
Compliance Factor	Calcium n=45	Placebo n=45	p-value
<b>Compliance &gt;80%</b>			
From randomization up to the last visit before pregnancy	10(22.23)	16(35.556)	0.817
From last visit before pregnancy to the 20-week visit	16(35.56)	32(71.12)	1.817
<b>Compliance &gt;50%</b>			
From randomization up to the last visit before pregnancy	16(35.56)	18(40)	3.817
Body mass index, kg/m <sup>2</sup>	17(37.78)	11(24.45)	4.817
From last visit before pregnancy to the 20-week visit	16(35.56)	5(11.12)	5.817

Pregnancy outcomes for both the Calcium and Placebo groups are in Figure 1, which

also allows for a direct comparison between the two groups. Pregnancy did not

occur for 75.6% of those taking Calcium and 80% of those taking a placebo (n=90 total). There was no statistically significant difference in pregnancy loss rates before 20 weeks of gestation between the Calcium and Placebo groups (26.7% and 35.6%, respectively). The frequencies of

livebirths (40% for Calcium, 35.6% for Placebo) and pregnancies that progressed to 20 weeks of gestation were also comparable between the two groups. The research group did not appear to affect pregnancy outcomes significantly.



**Figure 1: Pregnancy outcomes for all participants enrolled (n=90) according to study group**

The study found that preeclampsia was significantly reduced in Calcium group as compared to the Placebo group. Primary and secondary outcomes are broken down by treatment group (Calcium vs Placebo) in Table 3. Several outcomes were assessed, and RRs and p-values were calculated for each. Preeclampsia, the primary endpoint, occurred in 75.6% of the Calcium group and in 80% of the Placebo group, with no statistically significant difference between the two.

There were no statistically significant changes in the rates of other outcomes, including GBP, proteinuria, loss of pregnancy, GBP severity, preeclampsia onset, or maternal problems. However, compared to the Placebo group, more people in the Calcium group required postpartum of 7 days or longer. The investigation results showed no statistically significant differences between the two groups.

**Table 3: Primary and secondary outcomes according to study group**

Primary and Secondary Outcomes	Calcium n=45	Placebo n=45	p-value
Preeclampsia (as a proportion of all women randomizat)	0	6(13.34)	0.0488
Preeclampsia (primary outcome)	2 (4.44)	36(80)	0.039
Preeclampsia and or pregnancy loss at any gestation*	1 (2.23)	8(17.78)	0.0477
Gestational hypertension	6(13.34)	9(20)	0.005
Gestational proteinuria	13(28.89)	9(20)	0.005
Pregnancy loss at any gestation*	12(26.67)	10(22.23)	0.007
No pregnancy during the study period†	25(55.56)	22(48.89)	4.005
Severe gestational hypertension	21(46.67)	19(42.23)	0.740

Early onset preeclampsia (<32 weeks' gestation)	16 (35.56%)	15 (33.33%)	0.005
Severe preeclampsia	4 (8.89%)	6 (13.33%)	70005
Moderately severe thrombocytopenia	3 (6.67%)	4 (8.89%)	0.008
Uric acid greater than reference values	8 (17.78%)	7 (15.56%)	0.005
Renal failure (creatinine >120 mmol/L)	5 (11.11%)	6 (13.33%)	0.567
Liver failure	12 (26.67%)	9 (20.00%)	0.005
Eclampsia	9 (20.00%)	11 (24.44%)	0.005
Placental abruption	12 (26.67%)	9 (20.00%)	0.567
Pulmonary edema	9 (20.00%)	7 (15.56%)	0.644
Stroke	17 (37.78%)	15 (33.33%)	15.005
ICU admission >24 h	15 (33.33%)	13 (28.89%)	0.005
HELLP syndrome	6 (13.33%)	5 (11.11%)	0.644
Maternal death*	9 (20.00%)	8 (17.78%)	0.74
Participant hospital stay 7+ days after birth	7 (15.56%)	5 (11.11%)	0.019
Caesarean section	12 (26.67%)	11 (24.44%)	0.567
Birthweight <2500 g	11 (24.44%)	10 (22.22%)	0.644
Preterm birth (<37 weeks' gestation)	22 (48.89%)	24 (53.33%)	0.74
Early preterm birth (<32 weeks' gestation)	14 (31.11%)	12 (26.67%)	0.644
Apgar score <7 at 5 min	17 (37.78%)	19 (42.22%)	0.567
Perinatal death or admission to neonatal ICU >24 h	13 (28.89%)	12 (26.67%)	0.005
Stillbirth	14 (31.11%)	17 (37.78%)	0.065

## Discussion

Both preeclampsia and eclampsia are common sources of serious illness and mortality. Preterm delivery may be avoided, and preeclampsia may be less likely with calcium supplementation. This is a revision of a review that was previously released in 2014 to evaluate how calcium supplementation while pregnant affects hypertensive diseases of pregnancy and results for both the mother and the kid [12]. The study compared high-dose supplementation with Calcium (pregnancy at least 1 g of Calcium daily) with placebo in controlled trials (RCTs), and included cluster-randomized studies. They considered quasi-randomized studies, placebo-free trials, cointervention trials, and dosage comparison trials for Calcium at a low dosage. High-dose calcium supplementation (1 g/day) may reduce the risk of preeclampsia and other pregnancy complications, especially for women on low calcium diets premature delivery. Due to publication bias or the effects of limited studies, the treatment impact could be overstated [13]. Neither

stillbirth nor neonatal high care randomization, but the composite outcome of "maternal death or serious morbidity" is reduced. Calcium supplementation raised the likelihood of HELLP syndrome, however the risk was minimal overall. Small-scale, high-quality trials are needed to corroborate the minimal data on Low-dose calcium supplementation is associated with a decline in preeclampsia, hypertension, or neonatal critical care admissions [14].

A study was conducted to research the results of maternal and newborn outcomes, blood pressure, and calcium supplements during pregnancy. When primigravidas have a daily calcium consumption below the necessary dietary requirements, preeclampsia and premature birth seem less likely to occur [15]. A global focus is lowering the number of fatalities caused by hypertensive diseases during pregnancy. The high prevalence both conditions in low-income nations may be explained by poor dietary calcium intake. The severe effects calcium supplementation can lessen the risk of

preeclampsia during the second part of pregnancy, although its impact during placentation is unknown [16]. The idea that calcium supplementation before and throughout the first trimester (up to the hypothesis that preeclampsia is delayed until after 20 weeks of pregnancy is the one we looked at analyzing how dietary calcium supplements affect preeclampsia, high blood pressure and various other undesirable pregnancy outcomes [17]. Preeclampsia, both diastolic and systolic blood and both are significantly reduced when calcium supplementation is used during pregnancy. While taking Calcium throughout pregnancy is something preeclampsia-prone women should think about doing, additional patient outcomes are required to validate Calcium's effect on maternal and foetal morbidity [18].

There is much curiosity about how Calcium affects blood pressure control. Clinical trials, laboratory analyses, and epidemiologic studies have all demonstrated a connection between calcium & blood pressure that also exists during pregnancy [19]. According to the most recent data, it is evident that taking calcium supplements when pregnant decreases blood pressure [20]. Additionally, the incidence or gestation age of preeclampsia development may be influenced by the action of Calcium upon blood pressure. Furthermore, the influence on smooth-muscle relaxation shown in individuals receiving calcium supplements may impact the prevalence of preterm [21]. Calcium supplementation appears to impact the levels of renin and parathyroid hormone in the blood, which may modify intracellular calcium and cause the reported effect on smooth-muscle relaxation, however the exact mechanism for these effects is yet unclear. This impact could also oversee decreased uterine activity and a drop in the prevalence of preterm [22].

Preeclampsia and gestational hypertension can be avoided with calcium

supplementation. There needs to be more information on the ideal calcium dosage in addition to the conflicting results of the available research [23]. The ultimate analysis included an overall of 48 studies. All calcium supplementation dosages (low dose – all three studies; medium dose – 11 studies; high dose – 28 studies) decreased the prevalence of gestational hypertension among the low-risk population, but the medium dose (three studies) decreased the prevalence of gestational hypertension among high-risk groups [24]. Additionally, both low-risk and high-risk groups had the most significant reduction in gestational hypertension with a medium dosage of calcium supplementation. Preeclampsia was less common in the low-risk groups when calcium supplementation was given in medium (three trials) and high dosages (13 studies). However, in the low-risk population, a medium-dose supplementation with Calcium effectively avoided preeclampsia [25]. Due to the limitations of recent research regarding experimental design, result measurements, statistics, and evidence quality, the integrity and accuracy of the results were diminished. Therefore, high-quality studies with bigger sample sizes are needed to assess further the role of calcium supplementation in avoiding preeclampsia and gestational hypertension [26].

### Conclusion

The study has concluded that Calcium can significantly prevent preeclampsia in early pregnancy. However, the results of this complex research suggest that a more extensive study is required to adequately investigate the possible moderate effects of Calcium on preeclampsia. Researchers and policymakers should consider the trial's complexity and duration when deciding whether to conduct more research, which could involve a population-based approach. Taking this tack would allow for a more comprehensive analysis of calcium supplementation's impact on preeclampsia. The importance of the

prospective advantages and the possibility of performing a more extensive study should be considered when deciding whether to undertake future research. Pre-conception is a limitation of this trial because only participants who conceived and carried a pregnancy over 20 weeks were exposed to the primary outcome (preeclampsia). Researchers accounted for potential bias by comparing pregnancy rates between groups and performing follow-up analyses with varying denominators based on participants' reproductive status. Preeclampsia diagnosis rates may have been modified by the speed of early pregnancy loss, which may be affected by calcium supplements. As a composite secondary outcome, preeclampsia, pregnancy loss, or both were included to consider this.

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