Trials

STUDY PROTOCOL

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Calcium carbonate supplementation for the prevention of preeclampsia in high-risk pregnant women: a randomized clinical trial protocol

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Abstract

Background Preeclampsia (PE) is a significant cause of maternal mortality worldwide, affecting 2% to 8% of pregnancies. The World Health Organization recommends the use of low-dose acetylsalicylic acid (100 mg of aspirin) and 1.5 to 2 g of calcium carbonate during pregnancy to prevent PE. However, robust evidence supporting the efficacy of calcium supplementation is still needed. This study aims to assess the efficacy of calcium carbonate in preventing preeclampsia in high-risk pregnant women.

Methods A triple-blind, randomized clinical trial will be conducted at an outpatient clinic in Brazil between May 2024 and March 2026. Pregnant women at high risk of developing preeclampsia and with low dietary calcium intake will be randomly assigned to one of three groups: one group will receive calcium carbonate capsules (commercially available in Brazil) along with 100 mg of aspirin; the second group will receive calcium carbonate derived from *Crassostrea* sp. along with 100 mg of aspirin; and the control group will receive a placebo alongside 100 mg of aspirin. The primary outcome is the diagnosis of preeclampsia during pregnancy, while secondary outcomes evaluate maternal and fetal health indicators.

Discussion This trial seeks to generate evidence on the efficacy of calcium carbonate in preeclampsia prevention, with a focus on comparing industrial calcium carbonate with calcium carbonate sourced from *Crassostrea* sp., a more sustainable alternative.

Trial registration The study was approved by the Research Ethics Committee of the Federal University of Sergipe and registered in the Brazilian Registry of Clinical Trials (ReBEC), under the ID RBR-7hqhj3y. Registered on November 16, 2023.

Keywords Preeclampsia, Calcium carbonate, Pregnant women

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Administrative information

Title {1}	Calcium carbonate supplementation to prevent preeclampsia in high-risk pregnant women: protocol of a randomized clinical trial
Trial registration {2a and 2b}.	The trial was registered in the Brazilian Registry of Clinical Trials (ReBEC) under the ID RBR-7hqhj3y.
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Role of sponsor {5c}	The study sponsor and funder have approved the study design but do not participate in data collection, management, analysis, or interpretation of results, writing the report, or deciding whether to submit the report for publication.

Introduction

Background and rationale {6a}

Preeclampsia (PE) is a hypertensive disorder of pregnancy, strongly associated with both maternal and fetal mortality [1]. It is characterized by the onset of hypertension, proteinuria, or signs of organ dysfunction after the 20th week of gestation [2].

Currently, PE affects 2% to 8% of pregnant women, contributing to approximately 70,000 maternal deaths and 500,000 fetal deaths annually [3]. Low- and middle-income countries are particularly susceptible to PE and its severe complications [4]. In Brazil, the prevalence of PE mirrors global estimates, at around 6.7%. However, recent updates in diagnostic criteria have led to an increase in reported cases [5].

The World Health Organization (WHO) recommends low-dose acetylsalicylic acid and calcium supplementation (1.5 to 2 g/day) for pregnant women with low dietary calcium intake to prevent PE. Calcium supplementation, ideally in the form of calcium carbonate due to its better absorption, has been shown to reduce both the incidence and complications associated with the condition [6].

Despite the WHO guidelines, the widespread adoption of these interventions has encountered challenges, particularly related to the cost and logistics of calcium carbonate supplementation. The recommended dosage, which typically involves three to four doses of 500 mg/day, can increase treatment costs and negatively affect medication adherence [7].

The hypothesis of this study is that a daily dose of 1000 mg of calcium carbonate is sufficient to prevent preeclampsia in high-risk pregnant women. Additionally, the study investigates the feasibility of using calcium extracted from *Crassostrea oyster* species as a cost-effective and sustainable alternative.

Objectives {7}

Primary aim

(1) To evaluate the efficacy of calcium carbonate derived from Crassostrea sp. oyster shells compared to industrial-grade calcium carbonate in preventing preeclampsia in high-risk pregnant women.

Secondary aims

(1) To estimate adherence to calcium supplementation among pregnant women.
(2) To develop a calcium carbonate pharmaceutical dosage form from *Crassostrea* sp. oysters.
(3) To identify maternal morbidity and mortality, as well as fetal and neonatal outcomes.

Trial design {8}

To achieve this objective, a triple-blind, randomized controlled clinical trial (RCT) with a 1:1:1 allocation ratio will be conducted. The study will compare the efficacy of two calcium carbonate formulations with identical dosages but different sources (inorganic and organic) against a placebo in preventing preeclampsia in high-risk pregnant women. This trial will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines and adhere to the SPIRIT Checklist for Trials.

Methods: participants, interventions, and outcomes

Study setting {9}

This single-center study will be conducted at the outpatient clinic of the Public Health Center for Comprehensive Women's Health Care, located in Northeast Brazil, recognized as a referral center for managing patients with preeclampsia.

Eligibility criteria {10}

Pregnant women who meet the following criteria will be included in the study:

(1) Pregnant women who are up to the 20th week of gestation at the study baseline
(2) Presence of one or more risk factors for PE
(3) Sociodemographic characteristics associated with an increased risk of PE
(4) Low dietary calcium intake

Exclusion criteria

Pregnant women who present any of the following conditions will be excluded:

(1) Known placental abnormalities
(2) Current pregnancy resulting from IVF
(3) Regular use of platelet-active drugs
(4) Known fetal abnormalities
(5) Documented uterine bleeding within 1 week prior to screening
(6) Uterine malformations
(7) Sickle cell anemia
(8) Maternal age under 15 years

Who will provide informed consent? {26a}

Participants will be systematically approached by the researcher, who will explain all the steps of the study in detail. Once the pregnant women fully understand the study and agree to participate, they will sign the informed consent form. The confidentiality and anonymity of all participants will be safeguarded, in accordance with the Confidentiality and Secrecy Agreement signed by the research team.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

The informed consent form will clearly explain that medical records may be reviewed, and biological samples and personal data will be analyzed as part of the research.

Interventions

Explanation for the choice of comparators {6b}

Control group

Patients in the control group will receive 100 mg of acetylsalicylic acid along with a placebo, both administered in two daily doses. Acetylsalicylic acid is a proven medication for preventing preeclampsia [8].

Intervention description {11a}

Intervention group

The intervention groups will be designated as EG I and EG II. Patients in EG I will receive daily doses of 1000 mg of calcium carbonate (commercial grade), divided into two doses of 500 mg, along with 100 mg of acetylsalicylic acid, encapsulated in hard gelatin capsules. Patients in EG II will receive 1000 mg of calcium carbonate derived from *Crassostrea sp.* oysters, also divided into two doses of 500 mg, alongside 100 mg of acetylsalicylic acid in gelatin capsules.

The calcium carbonate extracted from *Crassostrea* sp. oyster shells will be developed by the Federal University of Sergipe in collaboration with the Federal University of Alagoas. The handling of capsules will follow the guidelines in the Brazilian Pharmacopoeia (6th ed., 2019) and the Brazilian Technical Response Service (SBRT, 2012). To ensure quality, the capsules will undergo rigorous testing, including evaluations of visual characteristics such as color, deformities, and the presence of foreign particles in the formulation.

In Brazil, calcium carbonate is primarily available as mass-produced capsules from pharmaceutical companies. Although not prohibitively expensive, calcium carbonate capsules are not among the least costly medications. Additionally, the country possesses untapped natural resources, particularly related to sustainable sources [9]. Calcium carbonate can be sourced from mollusk shells found along the Brazilian coast, which are typically discarded and not utilized by fishing communities. These renewable sources are environmentally integrated and, through collaborations between local communities, companies, and universities, calcium carbonate powder from these sources is being evaluated for its purity and pharmacopoeial properties and tested in pharmaceutical formulations [10].

Criteria for discontinuing or modifying allocated interventions {11b}

If patients experience any adverse reactions to the medications, they will be monitored, and, depending on the severity, may be excluded from the study. Additionally, participants retain the right to withdraw from the research at any time, regardless of the reason.

Table 1 Secondary outcomes that may be related to preeclampsia

Maternal
Early preeclampsia (before 32 weeks of gestation);
Severe preeclampsia—blood pressure ≥ 160/110 mmhg;
Gestational hypertension (diastolic blood pressure ≥ 90 mmHg on two occasions 4 h apart, or ≥ 110 mmHg once, and/or systolic blood pressure ≥ 140 mmHg on two occasions 4 h apart, or ≥ 160 mmHg once, after the 20th week of pregnancy);
Pregnancy loss before 20 weeks of gestation;
Pregnancy loss/stillbirth at any gestational age;
Gestational proteinuria;
Premature placental abruption;
Bleeding in the second half of pregnancy;
Maternal death;
Admission to the intensive care unit (ICU) > 24 h;
Acute renal failure (serum creatinine > 120 mmol/l or as defined by study authors);
Pulmonary edema;
HEELP syndrome;
Chronic venous disease;
Eclampsia;
Low medication adherence.
Fetal
Intrauterine growth restriction—estimated fetal weight < 10th percentile;
Birth weight < 2500 g;
Premature birth (< 37 weeks of gestation);
Early preterm birth (< 32 weeks of gestation);
Apgar scored less than 7 min;
Admission to the neonatal ICU for 24 h or more;
Stillbirth;
Fetal death or neonatal death before discharge;
The neonate is small for gestational age.

Strategies to improve adherence to interventions {11c}

To improve medication adherence, pharmacists will provide ongoing support, explaining the importance of the treatment and addressing any questions. Weekly phone calls will also be made to each patient to follow up on their treatment progress.

Medication adherence will be measured using the Brief Medication Questionnaire (BMQ), a tool that assesses barriers to adherence, beliefs about the regimen, and recall of drug treatment from the patient's perspective.

Relevant concomitant care permitted or prohibited during the trial {11d}

Participants who were on other medications prior to or during pregnancy will continue their treatments as prescribed, provided these do not interfere with the study interventions. In the event of potential drug-drug interactions, a case-by-case evaluation will be conducted to assess the safety and feasibility of continued participation. Patients will be monitored during each prenatal consultation, where adherence to the study protocol will be assessed. Non-adherence to the allocated intervention will result in withdrawal from the trial.

Provision for post-trial care {30}

All participants who complete the study, whether regularly or prematurely (due to serious adverse effects or ongoing adverse events such as abnormal laboratory results or vital signs), will be referred to the healthcare team for continued monitoring, and full support will be provided.

Outcomes {12}

Primary outcomes

Incidence of preeclampsia.

Secondary outcomes

Table 1 presents maternal and fetal results that may be related to the effects of calcium carbonate and will be observed throughout the study.

	STUDY PERIOD			
	Enrolment	Allocation	Post-allocation	Close-out
TIMEPOINT	-t1 May (2024) to june (2025)	0 May (2024)	t1 May (2024) to March (2026)	t2 November (2025) to March (2026)
Eligibility screen	x			
Informed consente	x			
Participant approach	x			
Data collection	x			
Allocation		x		
INTERVENTIONS:				
ASPIRIN +$CaCO_3$ (extracted from oyster)			x	
ASPIRIN +$CaCO_3$			x	
ASPIRIN+ Placebo (group control)			x	
ASSESSMENTS:				
Assessment of outcomes				x
Data analysis				x

Fig. 1 Representation of the data collection stages (SPIRIT figure)

Participant timeline {13}

Data collection will occur from May 2024 to March 2026, with participant recruitment continuing until June 2025. Monitoring will be conducted throughout the entire data collection period. The research steps are outlined in Fig. 1.

Sample size {14}

A sample size of at least 156 patients per group was calculated to provide 80% power to detect a 50% reduction in the incidence of preeclampsia (PE), assuming that 30% of high-risk pregnant women will develop PE. A two-sided *t*-test with a familywise α level of 0.05 will be used. To adjust for multiple comparisons among the three groups, the Sidak correction will be applied, yielding an adjusted α level of approximately 0.017 for each comparison. Considering these adjustments, the total required sample size is approximately 468 participants, with 156 in each of the three groups (two intervention groups and one placebo group). To accommodate an anticipated dropout rate of 10%, the sample size per group is increased to approximately 173 patients. This adjustment ensures that the study will maintain adequate power to detect a statistically significant difference while minimizing the risks of type I and type II errors.

Recruitment {15}

Participants will be systematically approached at the prenatal care facility and invited to participate in the study. The research procedures will be thoroughly explained to all potential participants before enrollment.

Assignment of intervention: allocation

Sequence generation {16a}

Eligible patients will be randomly assigned to one of the study groups through a central allocation system. This will be done using a random sequence generated by the PEPI - Statistical & Statistical Software's Calc Suite. Sealed, opaque envelopes containing the group assignments will be used to ensure allocation concealment.

Concealment mechanism {16b}

An intention-to-treat analysis will be employed. Capsules containing placebo will be visually indistinguishable from those containing calcium supplements. Participants will receive free calcium carbonate supplementation (industrialized or from *Crassostrea* sp.) along with acetylsalicylic acid at each prenatal consultation, along with instructions for use.

Implementation {16c}

Randomization will be managed by a pharmacist who is not involved in the study. Treatment codes will be generated for each intervention. Labeling of the products will be handled by trained personnel who are not part of the study, ensuring blinding is maintained.

Assignment of intervention: blinding

Who will be blinded {17a}

This study will be triple-blinded, meaning that the participants, the researchers, and the statistical analysis team will be unaware of the group assignments.

Procedure for unblinding if needed {17b}

In the event of an emergency requiring unblinding, the researcher overseeing the study will have access to the blinding codes. The breaking of blinding will be documented, and confidentiality will be maintained unless required for patient safety.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Prior to enrollment, participants will complete a pre-coded instrument designed to capture sociodemographic, obstetric, and nutritional data, allowing identification of those at high risk for developing preeclampsia (PE). To estimate calcium intake, the "Calcium Calculator" app from the International Osteoporosis Foundation (IOF) will be used. This tool estimates weekly calcium intake and compares it to the recommended levels. To reduce recall bias, participants will be encouraged to (a) immediately record their food intake using a food diary, (b) receive brief guidance on how to use the diary, and (c) obtain feedback on their entries to allow for corrections.

Data on factors strongly associated with a high risk of preeclampsia, such as antiphospholipid antibody syndrome, previous preeclampsia, chronic hypertension, pregestational diabetes, and BMI > 30, will be gathered from medical records. Sociodemographic characteristics, including maternal age, household income, and education level, which may also contribute to the risk of PE, will be collected via structured questionnaires.

Plans to promote participant retention and complete follow-up {18b}

To promote participant retention and ensure complete follow-up, participants will receive their monthly treatment supply during prenatal consultations. They will also have a session with a pharmacist to address any issues related to medication adherence.

Data management {19}

Data will be collected in person using password-protected notebooks or tablets. All completed forms will be securely stored on a password-protected server, with regular backups and software updates. Research materials and data will be archived under the main researcher's responsibility for up to 5 years.

Confidentiality {27}

The lead researcher will ensure that all research data is stored securely, with confidentiality and privacy protected in accordance with applicable laws and regulations. Participants will remain anonymous throughout the study.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetics or molecular analysis in this trial/future use {33}

Not applicable; no biological samples will be collected in this study.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Primary analyses will follow the intention-to-treat principle. Data will be presented as proportions, means with standard deviations (SD), or medians with interquartile ranges, depending on the distribution's normality, which will be tested using the Shapiro-Wilk test. SPSS 10.5 software will be used for analysis. Bivariate analysis will be conducted using either Student's t-test or the Mann-Whitney U test, based on normality assumptions. The chi-square test or Fisher's exact test will be used when applicable. A p-value of < 0.05 will be considered statistically significant.

Interim analyses {21b}

An interim analysis will be conducted after one-third of the participants are enrolled to evaluate safety and efficacy.

Methods for additional analyses (e.g., subgroup analyses) {20b}

There are no additional analyses planned for this study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Patterns of missing data will be evaluated to determine if they are missing completely at random (MCAR), at

random (MAR), or not at random (MNAR). Multiple imputation using chained equations will be employed to handle missing data, with at least 20 imputations to minimize variability. Sensitivity analyses will be conducted to ensure the robustness of the findings.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

There is no plan to provide public access to the dataset or statistical code at the participant level. However, all results, whether positive or negative, will be published. Funding sources will not influence the reporting of results.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The study team consists of pharmacists, pharmacy interns, physicians, nurses, senior researchers, and a doctoral student with clinical pharmacy experience. The senior researcher has extensive experience with clinical trials. Prior to study initiation, all team members will undergo training, and weekly meetings will be held throughout the study to ensure quality control and prevent errors.

Composition of the data monitoring committee, its role, and the reporting structure {21a}

Researchers responsible for data collection will also monitor for adverse reactions. The principal investigator will meet monthly with the team to audit monitoring activities and adverse events. Based on these audits, recommendations regarding study continuation, modification, or termination will be made.

Adverse event reporting and harms {22}

The risks associated with this study are minimal, but potential adverse reactions, such as gastric discomfort or allergic responses to calcium supplements or acetylsalicylic acid, are possible. Gastric discomfort will be minimized through guidance on the timing of medication administration. In the event of an allergic reaction, patients will seek medical attention and be withdrawn from the study if necessary.

Frequency and plans for auditing trial conduct {23}

Audits and inspections may be conducted by the Brazilian Health Surveillance Agency. Auditors will have access to all data, raw materials, informed consents, and any other clinical trial documents deemed necessary.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Currently, there are no planned changes to the study. If amendments become necessary in the future, the researchers will notify the ethics committee accordingly.

Dissemination plans {31a}

Scientific articles resulting from this study will be published in peer-reviewed journals, thereby contributing to the global body of research knowledge and facilitating the dissemination and comparison of information.

Discussion

Pregnancy is a state of high calcium demand, as intestinal absorption increases markedly to support fetal needs. Approximately 30 g of calcium is transferred to the fetus during gestation, and several hormonal changes occur to maintain calcium homeostasis throughout pregnancy. To meet this demand, it is considered prudent to administer calcium carbonate daily at a dose of 1.0 to 1.5 g to pregnant women from the initial contact until delivery (11; 6; 12).

The World Health Organization recommends a daily dose of 1.5 to 2.0 g of calcium carbonate, divided into three to four doses of 500 mg each. Despite some evidence supporting the efficacy of this treatment in preventing preeclampsia, it is not widely implemented, primarily due to the cost and logistical challenges associated with the multiple administrations required [7].

In this study, calcium carbonate will be administered at a dose of 500 mg once daily. Additionally, we will develop a calcium carbonate supplement derived from the shells of *Crassostrea* oysters, which will be used for pregnant women at risk of preeclampsia. *Crassostrea* oyster shells will be sourced from the coast of Alagoas, Brazil. Oysters are commonly consumed in the Brazilian coastal regions, especially in the Northeast. Due to insufficient awareness regarding proper disposal, shells are often discarded with domestic waste, leading to environmental issues such as siltation in rivers and beaches [9]. Thus, repurposing oyster shells to produce calcium carbonate represents a sustainable alternative to calcium carbonate obtained from traditional extractive sources.

The efficacy of calcium carbonate derived from *Crassostrea* oysters, administered at a dose of 1 g (500 mg twice daily), will be evaluated in this study. This approach aims to reduce costs and improve treatment adherence. Furthermore, the study will assess the real benefits of industrial-grade calcium carbonate (at a

dose of 1 g) in mitigating fetal and maternal complications in pregnant women with risk factors for preeclampsia.

Eligibility criteria were carefully selected to include factors that increase the incidence of preeclampsia (PE) in the study population, given that PE risk factors are relatively common. Socioeconomic factors also play a role in diagnosis and progression, as lower-income populations have less access to healthcare services [11].

Evidence suggests that high calcium intake correlates with a lower incidence of PE, indicating that inadequate calcium intake is directly associated with a higher risk of developing PE [12]. This study will measure calcium intake using the calcium application calculator, a reliable tool developed by the International Osteoporosis Foundation (International Osteoporosis Foundation, 2024).

The study will test the efficacy of calcium carbonate derived from *Crassostrea* sp., a renewable byproduct, as an alternative to nonrenewable limestone sources [13]. Additionally, evaluating an intermediate dose of calcium carbonate may provide more evidence on the efficacy of smaller doses and potentially enhance patient compliance by reducing the daily dosage. Adherence will be monitored using the Beliefs about Medicines Questionnaire (BMQ) to assess medication adherence and identify reasons for non-adherence.

Finally, a triple blinding approach was chosen for this study to enhance result reliability and minimize bias, including in the selection of interventions. While the primary outcome will be the diagnosis of PE, several secondary outcomes will be evaluated to provide a comprehensive understanding of calcium carbonate's role in preventing PE, with some of these selected outcomes not previously measured in other studies.

Thus, it is expected—through rigorous observation of medication adherence during the study and other methodological aspects described above—to evaluate the effect of calcium carbonate on the manifestation of preeclampsia in high-risk patients, as well as assess the feasibility of calcium carbonate obtained from *Crassostrea* oysters.

Trial status

Date recruitment began: May 30, 2024.

Approximate date of recruitment completion: June 30, 2025.

Patient follow-up: Mar 30, 2026.

Abbreviations

BMQ	Brief Medication Questionnaire
CONSOT	Consolidated Standards of Reporting Trials
IOF	International Osteoporosis Foundation
PE	Preeclampsia
ReBEC	The Brazilian Registry of Clinical Trials
UFS	Federal University of Sergipe

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Authors' contributions {31b}

CRVO, CLR, and ADOF: conceptualization. CRVO, CLR, and ARM: data curation. ARM, and ADOF: formal analysis. CRVO and ADOF: investigation. CRVO, CLR, and ARM: funding acquisition. CRVO and ADOF: methodology. CRVO AND ADOF: project administration. CRVO and ADOF: resources. ADOF: supervision. ADOF, CRVO, SJFN, and ARM: validation. CRVO, ARM, and ADOF: visualization. CRVO, CLR, ARM, SJFN, and ADOF: writing—original draft. CRVO, CLR, ARM, SJFN, and ADOF: writing—review and editing.

Funding {4}

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Availability of data and materials {29}

All the data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate {24}

The study protocol was approved by the ethics committee of the Research Ethics Committee of the Federal University of Sergipe (UFS) (CAAE: 69599023.6.0000.5546). This study was carried out following the ethical guidelines of the norm contained in CNS Resolution n° 466/12, which is based on the Declaration of Helsinki principles.

Consent for publication {32}

All authors consent to the publication of this protocol. All participants signed an informed consent form before participating in the study.

Competing interests {28}

The authors declare that they have no competing interests.

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