

## **SCOPE REVIEW: A COST-EFFECTIVE ANALYSIS OF CALCIUM IMPLEMENTATION IN PREGNANT WOMEN WITH PRE-ECLAMPSIA**

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**Abstract: Introduction:** Among the hypertensive syndromes, eclampsia and preeclampsia, according to the Ministry of Health, are one of the main causes of maternal mortality. There are studies indicating that low-dose (< 1 g/day) calcium supplementation would have similar effectiveness to high doses (> 1 g/day) in reducing preeclampsia, but there are few economic evaluation studies that demonstrate that this technology in health it is cost-effective. Objective: To characterize cost-effective economic evaluation studies with calcium supplementation in the prevention of preeclampsia in pregnant women. Method: Scope review, protocol registration on the OSF platform, selection of studies considering the gray literature and the following bases; VHL, EMBASE, PUBMED, SCOPUS, without time and language limits, selection by title and abstract with Rayyan app. The selected studies were read in full and analyzed considering the 22-item checklist of the PRISMA - ScR. **Result:** N=101 publications were found, duplicates were removed, leaving N=84, after screening the pair of blind researchers, we selected N=08, leaving a final sample of 4 articles. In the description of the checklist evaluation, CHEERS/2022, the items included in the publications N=1 and N=2 presented n=16/28;57% versus n=25/28;89%, both present the same type of prediction and modeling, but contemplate different quantity and methodological quality. Meanwhile, the studies N=3 and N=4 present n=20/28;71% versus n=21/28;75% with different types of predictions, despite these items of methodological rigor being close. These consolidated economic assessments of 4 articles describe information such as: health outcomes; quantification of costs; modeling; generalization of results; uncertainties among others. **Conclusion:** The cost dimensions, limitations in cost-effective assessments and their consequences in the face of comparison

options to offer greater return on the outcome directed to the financing of this technology, showed that the N=2 study presents better methodological rigor and greater impact analysis budget contributing to successful decision making.

**Keywords:** Pregnancy, Preeclampsia, Cost-effectiveness, Calcium.

## INTRODUCTION

In 2017, around 295,000 women died during pregnancy, childbirth and after childbirth. The global maternal mortality rate is very high and is concentrated in developing countries, of those deaths about 94%, in many cases, are preventable (UNFPA et al., 2019). The main complications in pregnancy, childbirth and after childbirth, responsible for almost 75% of maternal deaths are: severe bleeding, unsafe abortion, infections, childbirth complications and preeclampsia (PE) and eclampsia (SAY et al., 2014).

To address this issue, the United Nations (UN) established global commitments with targets by 2030, included in the Millennium Declaration; the SDG3 target is about reducing maternal and child deaths and improving maternal health through the application of good health practices. The current maternal and infant mortality indicators in Brazil are high compared to those of developed countries, reflecting the inequity in access to quality health services determined by the country's level of development (UN, 2018).

PE is a multisystem disorder of pregnancy characterized by multi-organ damage and hypertension, which occurs in 3-5% of pregnancies. It is estimated that it causes at least 42,000 maternal deaths a year. Two strategies are being used to decrease the short- and long-term adverse outcomes caused by preeclampsia; a) perform a screening for PE associated with the performance of auxiliary tests to exclude the diagnosis and, b) drug

prevention of this condition, with the use of aspirin, calcium, among other agents, despite the lack of strong evidence on the effectiveness of this type of intervention (CHAPPELL et al., 2021).

Considering the Cochrane systematic review, there is good quality evidence indicating that supplementation of high doses (1.5 g-2.0 g) of calcium (Ca) is effective in reducing the incidence of hypertensive syndromes in pregnancy (HOFMEYER GJ, 2017). ). Since 2011, the WHO has recommended this practice in places where the population has a low intake of dietary Ca (< 900 mg/day. Brazilian women fall into this group, according to data from the national survey on food consumption, the national average of consumption of Dietary Ca for these adult women (19-59 years old) is 443.20 mg/day, and 90.3% of them have Ca intake below the recommended for their age group (IBGE, 2011).Ca supplementation is not routinely prescribed by physicians in the Unified Health System (SUS) network, despite the availability of Ca being free, demonstrating a lack of knowledge of the benefits of Ca supplementation to prevent PE, as a result of the absence of evidence-based practice in maternal health (CAMARGO et al. al., 2013.) To implement calcium supplementation in the SUS, it is necessary, in addition to clinical evidence, to carry out studies of good methodological quality and cost-effectiveness on this health technology.

Economic evaluation and cost-effectiveness studies help decision making in the incorporation of new technologies, especially when we find that the financial resources necessary to face many Public Health issues are scarce and finite. From this perspective, it is possible to identify a vertical increase in cost-effectiveness assessment studies focused on health expenditures in recent years. and managers have been pressured

to observe the results of these studies when choosing to allocate resources in health technology (MORAZ et al., 2015). Therefore, the importance of characterizing cost-effective economic evaluation studies with calcium supplementation in the prevention of preeclampsia in pregnant women.

## METHOD

This is a Scoping review registered on the Open Science Framework - OSF platform (osf.io/8rwn7). Which aims to answer the guiding question of a review adapted from key elements suggested by Population, Concept and Context - PCC (P: pregnant, C: cost-effective and C: calcium supplementation): Is it cost-effective to implement calcium for pregnant women with pre eclampsia?

The CHECK LIST - PRISMA - ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist parameters (TRICCO et al., 2018) was applied to prepare the scope review with 22 items considered mandatory.

## SEARCH STRATEGY

The search strategies took place in January 2022, identifying the evidence, without time and language limits. The extraction included the following bases: VHL, EMBASE, PUBMED, SCOPUS, also researching national dissertations and theses through the CAPES theses database and Google Scholar. Table 01 shows 4 databases that describe the search strategies.

The selection of N=101 studies observed, with the aid of the Rayyan tool, the pre-established inclusion and exclusion criteria (OUZZANI et al., 2016) and the data analysis was characterized by the detailed description of the items: author and year, country, prediction types, results and article quality checklist. This classification of selected articles

Item	Pregnancy	Calcium Pre-Eclampsia prevention	Cost-Effectiveness
BVS	(tw:(pregnancy OR pregnancies OR gestation)) AND (tw:(Calcium Pre-Eclampsia prevention)) AND (tw:(cost-effectiveness))		
EMBASE	('pregnancy' OR 'pregnancy'/exp OR pregnancy OR pregnancies OR 'gestation' OR 'gestation'/exp OR gestation) AND 'calcium' AND 'pre eclampsia' AND 'prevention' AND ('cost effectiveness'/exp OR 'cost effectiveness')		
PUBMED	("Pregnancy"[Mesh] or "Pregnancies" or "Gestation") AND ("Calcium"[MeSH] OR (Blood Coagulation Factor IV) OR (Coagulation Factor IV) OR (Factor IV, Coagulation) OR (Calcium-40) OR (Calcium 40) OR (Factor IV))) AND ("cost-effectiveness analysis"[MeSH Terms] OR cost-effectiveness[Text Word] OR (Analyses, Cost-Benefit) OR (Analysis, Cost-Benefit) OR (Cost-Benefit Analyses) OR ( Cost Benefit Analysis) OR (Analyses, Cost Benefit) OR (Analysis, Cost Benefit) OR (Cost Benefit Analyses) OR (Cost Effectiveness) OR (Effectiveness, Cost) OR (Cost-Benefit Data) OR (Cost Benefit Data) OR (Data, Cost-Benefit) OR (Cost-Utility Analysis) OR (Analyses, Cost-Utility) OR (Analysis, Cost-Utility) OR (Cost Utility Analysis Cost-Utility Analyses) OR (Economic Evaluation) OR ( Economic Evaluations) OR (Evaluation, Economic) OR (Evaluations, Economic) OR (Marginal Analysis) OR (Analyses, Marginal) OR (Analysis, Marginal Marginal Analyses) OR (Cost Benefit) OR (Costs and Benefits Benefits and Costs) OR (Cost-Effectiveness Analysis) OR (Analysis, Cost-Effectiveness) OR (Cost Effectiveness Analysis))		
SCOPUS	(cost-effectiveness) AND ((pregnancy OR pregnancies OR gestation)) AND ( TITLE-ABS-KEY (calcium AND for AND pre-eclampsia AND prevention))		

Table 01 - Database search strategies, Manaus-AM, 2022.

Source: Own Author, 2022

describes and presents a summary about the theme.

## RESULT

N=101 studies were found, duplicates were removed, we identified N=84 studies, which were screened by reading titles and abstracts by a blind team and, in cases of discrepancy, a third author collaborated to standardize the consensus, totaling the selection of N=08 for full reading of the articles, resulting in the final sample of 4 publications. Figure 01 shows the search and selection flowchart of the scoping review studies, according to the JBI recommendations, according to a checklist adapted from PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (TRICCO et al., 2018)

The main findings found in the evidence in the databases occurred between 2016 and 2019 and bring a broad view of the concepts linked to the guiding question and objectives delimited by the review.

To analyze the methodological quality of the economic studies, the CHEERS/2022 tool (new checklist and report of the explanation and elaboration task force) was chosen (HUSEREAU et al., 2022), which contains 28 items accompanied by descriptions to evaluate the relevance and quality reporting of economic health assessment articles with the criteria defined to better meet the focus and outcome of the selected studies in full, which are summarized in Table 02.

The publications (1, 2, 3 and 4) analyzed on the subject are international and deal with specific evidence of economic evaluation of cost-effectiveness of low-dose calcium supplementation during pregnancy, noting similarities in the studies because they are carried out in public institutions locations.

Based on the characteristics described by the evaluation of the checklist, CHEERS/2022 (HUSEREAU et al., 2022), the items included in the publications N=1 and N=2 presented n=16/28;57% versus n=25/28;

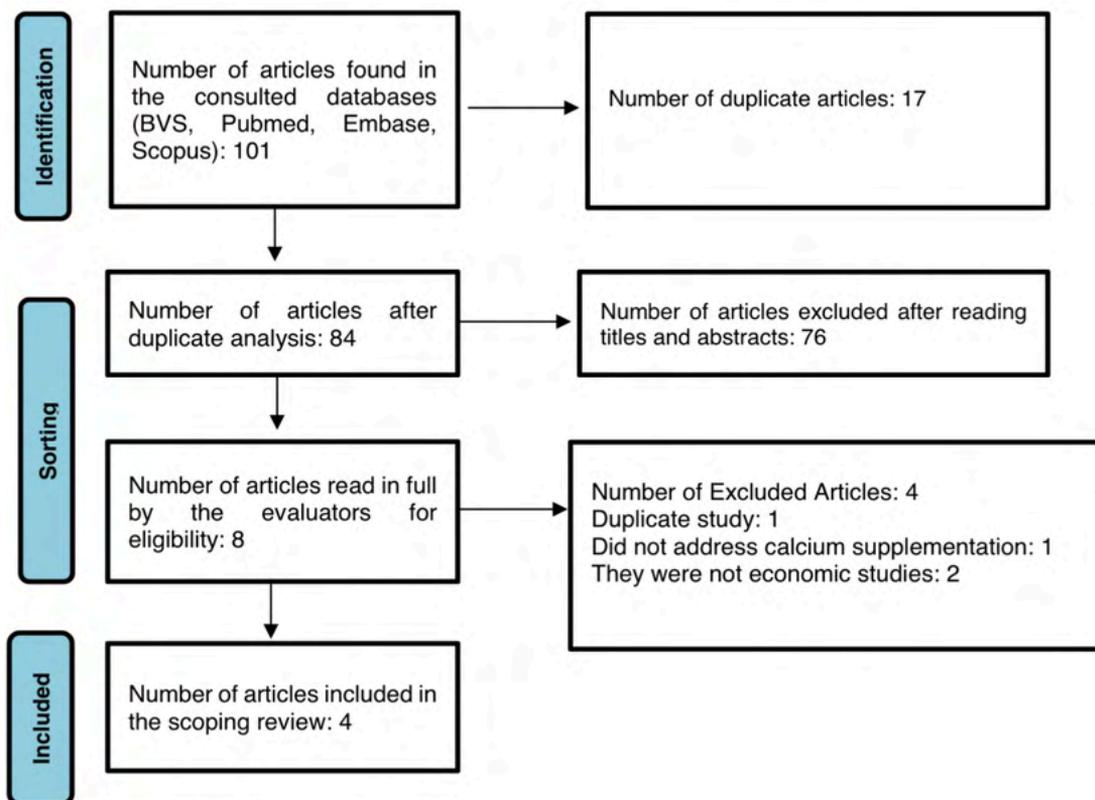


Figure 1 - Flowchart of article selection for the Scope Review.

Source: Adapted from TRICCO et al., 2018.

Item	Authors, Year	Country	Prediction Type	Results	Checklist
N=1	Chicaiza Becerra L.A. et. al, 2016	Coloimbia	Analytical Statistical Method using decision tree (TreeAge)	Administering calcium is the dominant alternative to non-intervention. If the incidence of preeclampsia is < 51.7 per 1,000 pregnant women or the cost of a 600 mg calcium tablet is more than COP (Colombian Pesos) \$507.85, the calcium supplement is no longer a cost-effective alternative in Colombia to a threshold of 3 times the 2013 GDP per capita (COP \$45,026,379) per AVG.(life years gained). The Ca supplement has greater effectiveness in AVG and lower average cost per patient versus no intervention.	16/28
N=2	Isabelle Feldhaus et. al, 2016	Nepal	Statistical and Analytical Model, using a decision tree (TreeAge)	Costs for introducing calcium in addition to MgSO4 were \$44,804, while costs to support ongoing program implementation were \$72,852. These amounts correspond to a program cost per person per year of \$0.44, collectively. The calcium program corresponded to a social cost per DALY avoided of \$25.33 (\$25.22-29.50) compared to MgSO4 treatment. Primary cost drivers included fee for facility delivery, costs associated with hospitalization, and the probability of developing PE/E. Adding calcium to the standard of care corresponds to slight increases in effect and cost, and has an 84% probability of cost. -effectiveness above a DDP (standard deviation) threshold of \$40 USD (US Dollar) when compared to standard of care alone.	25/28

Table 02 - Studies of cost-effectiveness economic evaluations in pregnant women supplemented with calcium for the prevention of preeclampsia, Manaus-AM, 2022.

Source: Own Authorship, 2022.

Item	Authors, Year	Country	Prediction Type	Results	Checklist
N=3	Linda J. E. Meertens et. al, 2017	Netherlands	Simple Decision Statistical and Analytical Model (Excel)	In current care, PE complicates 3% of all pregnancies (3,000/100,000). Base-case analysis indicated that if calcium supplementation is advised to pregnant women (n=100,000) (scenario 1), 763 cases of PE will be avoided (ie, a relative reduction of 25%). The estimated net financial benefit (savings minus calcium supplement costs) was €4,621,465 per 100,000 pregnant women.	20/28
N=4	Solomon Tessema Memirie et. al, 2019	Ethiopia	Statistical Model, Static Life Table Model	They identified that 12 of the 13 interventions included in the analyzes were highly cost-effective. Interventions targeting newborns, such as neonatal (institutional) resuscitation, kangaroo mother care, and treatment of neonatal sepsis with injectable antibiotics were the most cost-effective interventions with incremental cost-effectiveness ratios of \$7, \$8, and US \$17 per DALY avoided, respectively. Obstetric interventions (induction of labor, active management of the third stage of labor, management of preeclampsia/eclampsia and maternal sepsis, treatment of syphilis and tetanus toxoid during pregnancy) and safe abortion cost between \$100 and \$300 per DALY avoided. Calcium supplementation for preeclampsia and eclampsia prevention was the least cost-effective, with a cost per DALY of about \$3100. Many of the MNH interventions reviewed were highly cost-effective; evidence that can guide the review of the essential health services package underway in Ethiopia. The analysis also shows that calcium supplementation does not appear to be cost-effective in that environment.	21/28

Table 02 - Continuation. Studies of cost-effectiveness economic evaluations in pregnant women supplemented with calcium for the prevention of preeclampsia, Manaus-AM, 2022

Source: Own Author, 2022

89%, both show the same type of prediction and modeling, but with different statistical data, while studies N=3 and N=4, show n=20/28;71% versus n=21/28;75% with types of different predictions, despite these items of methodological rigor being close to each other. These economic assessments consolidated in the articles (1,2,3 and 4) described information such as: health outcomes; cost quantification; modeling; generalization of results; v) uncertainties, among others.

## DISCUSSION

From the findings selected in this study, we identified technological evidence in health policies on the implementation of calcium for the prevention of preeclampsia in countries such as; Colombia, Nepal, the

Netherlands and Ethiopia, which differ from Brazil in presenting a cost-effectiveness analysis. (CHICAÍZA-BECERRA et al., 2016; FELDHAUS et al., 2016; MEERTENS et al., 2018; MEMIRIE et al., 2019).

In the first three studies we identified that calcium supplementation is cost-effective for preeclampsia compared to no intervention. The study N=1 used as a measure of effectiveness years of life gained (AVG), the studies N=2 and N=4 used as a measure of effectiveness disability-adjusted life years (DALY's), N=3 does not deal with this measure and, considering that the assumption of the quality of years of life saved is relevant to the process, when not included in the cost-effectiveness analysis, the study has a limitation that makes it difficult for the manager to make the best

choice or decision-making (SANDERS et al. , 2016 ;BARRETO et al., 2017).

For the prediction method, mathematical and statistical models were used. The studies N=1 and N=2 chose the TreeAge tool for the decision tree elaboration, while N=3 chose the Excel tool for the decision tree elaboration and N=4 used a static life table model. Although Microsoft Excel as well as TreeAge are software programs used for analytical decision modeling, the latter performs better to build Markov models and decision trees to perform cohort simulations, given its predominance in the published literature on modelling. cost-efficiency (HOLLMAN C et all, 2017).

It must be noted that the quality of the economic study, with regard to costs and description, was better presented in the article N=2, where the comparison of the benefits produced by the consumption of supplementation of calcium to standard of care showed a slight increase in effect and cost, and had an 84% probability of cost-effectiveness above a DDP threshold of \$40 USD when compared to standard of care without calcium implementation for pregnant women (FELDHAUS et al, 2016).

## CONCLUSION

The proposed scoping review characterized the evidence, in such a way that reliability is procedural and indicative of improvement in the area when we compare the efficiency analysis between supplementing or not supplementing calcium in pregnant women to prevent preeclampsia. Thus, when we consider the dimensions of cost and its consequences for health, as well as the cost-effective limitations given the options for comparisons to offer greater return on the outcome directed to the financing of this health technology, we predominantly observe that the publication N= 2 presents better methodological rigor and greater budgetary impact, contributing favorably to the success of a choice or decision-making.

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