Calcium Supplementation to Prevent Preeclampsia: Translating Guidelines into Practice in Low-Income Countries[1,2]

Moshood O Omotayo,[3]* Katherine L Dickin,[3] Kimberly O O'Brien,[3] Lynnette M Neufeld,[4] Luz Maria De Regil,[3,5] and Rebecca J Stoltzfus[3]

[3]Division of Nutritional Sciences, Cornell University, Ithaca, NY; [4]Global Alliance for Improved Nutrition, Geneva, Switzerland; and [5]Micronutrients Initiative, Ottawa, Canada

ABSTRACT

The WHO issued a strong recommendation that pregnant women be provided calcium supplements to prevent preeclampsia. This is the first recommended nutritional intervention to prevent this condition, a leading cause of maternal mortality globally. As health systems seek to implement this new intervention, a number of issues require further clarification and guidance, including dosage regimen, supplement formulation, and alignment with other antenatal nutritional interventions. We summarize key evidence on the above points and offer our views on good practices. Most developing countries have low calcium intake, so where habitual calcium intake is unknown, calcium supplements are likely beneficial. In our view, policymakers and program planners should consider adopting doses between 1.0 and 1.5 g elemental calcium/d, depending on the local average and variation in dietary calcium intake, logistical feasibility, and acceptability in the target population. Prudent practice would entail daily administration as calcium carbonate administered in divided doses of not >500 mg elemental calcium per dose. For ease of prescribing and adherence, calcium [as with iron and folic acid (IFA)] should be administered routinely to pregnant women from the earliest contact in pregnancy until delivery. Calcium's acute inhibitory effect on iron absorption translates to minimal effects in clinical studies. Therefore, to simplify the regimen and facilitate adherence, providers should not counsel that calcium and IFA pills must be taken separately. Although further research will shed more light on clinical and programmatic issues, policies can be implemented with ongoing revision as we continue to learn what works to improve maternal and newborn health. *Adv Nutr* 2016;7:275–8.

Keywords: calcium, iron, micronutrient supplements, preeclampsia, maternal nutrition, maternal health, neonatal health

Introduction

The WHO issued guidelines recommending routine calcium supplementation during pregnancy to prevent preeclampsia (1). Prominent obstetrics professional organizations have also issued statements about the efficacy of calcium supplementation for the prevention of preeclampsia in populations with low dietary intake and a high risk of preeclampsia (2–5). Globally, hypertensive disorders of pregnancy, which include preeclampsia, and constitute the second leading cause of maternal mortality (6). Calcium supplementation is a low-risk, relatively inexpensive preventive intervention suitable for widespread implementation in community-based and primary-care settings, and has the potential for substantial effects on maternal and newborn health.

Preeclampsia is a pregnancy-specific multi-systemic disorder characterized by proteinuria and the onset of hypertension during pregnancy (7, 8). Eclampsia is the occurrence of otherwise inexplicable convulsions or coma in a preeclamptic patient (7, 8). Preeclampsia is believed to be multifactorial in origin, with risk severity influenced by both maternal and fetal determinants (7). Delivery of the placenta is the only known cure for preeclampsia and eclampsia (7, 8).

The WHO guideline states that, "In populations where calcium intake is low, calcium supplementation as part of antenatal care is recommended for the prevention of preeclampsia among pregnant women, particularly among those at higher risk of hypertension." (1) This strong recommendation is based on moderate quality evidence from meta-analyses of randomized clinical trials that found that calcium supplementation prevented approximately one-half of preeclampsia cases (1). The guideline recommends daily administration of 1.5–2.0 g of supplemental

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*To whom correspondence should be addressed. E-mail: moo6@cornell.edu.

calcium from 20 wk of gestation onwards, and remarks that it is preferable to separate calcium and iron supplementation by several hours to minimize the possible negative effects of calcium on iron absorption (1).

This is an important recommendation. However, similar evidence-informed interventions such as iron and folic acid (IFA) supplementation during pregnancy have failed to meet expectations when scaled up, because of product composition, supply chain, and demand-related barriers that hamper implementation under routine delivery conditions (9). Thus, to realize the benefits of calcium and IFA supplementation, feasible and acceptable protocols for integration into existing antenatal care systems are essential.

We summarized evidence on key issues related to dose, regimen, and targeting of calcium supplementation in public health programs in low-income countries, because these are critical to program design. Although necessary to ensure effective program implementation, we did not focus on calcium supply chain and demand creation barriers, because program experience is, as yet, very limited.

Antenatal Calcium Supplementation to Prevent Preeclampsia

Ideally, a policy of routine supplementation should be preceded by an assessment of dietary calcium adequacy at the population level, enabling the intervention to be targeted to populations with diets low in calcium. However, the threshold of intake below which calcium supplements become efficacious remains unknown. Furthermore, habitual calcium intake is poorly characterized in many developing countries, where low calcium intake and maternal mortality are most common. Where it has been studied, habitual calcium consumption usually has been found to be low. For example, in a recent review of the dietary intake of pregnant women in low- and middle-income countries, 35 of 42 studies found mean calcium intake to be <900 mg/d, and this was consistent in studies from Asia, Africa, and Latin America (10). It is therefore reasonable to assume that mean population consumption is inadequate in most low-income country settings unless local dietary studies indicate otherwise.

Besides supplementation, food-based approaches and nutritional education are potentially sustainable and acceptable approaches to increasing calcium intake in pregnant women. However, data are lacking for the development of evidence-informed policy and program recommendations on food-based approaches to delivering calcium for prevention of preeclampsia. The feasibility of meeting requirements through dietary counseling alone is remote, given the limited access to calcium-rich foods in many low-income settings. Combining dietary counseling with supplementation, however, is sensible.

Supplement Formulation

Several calcium salt formulations are currently available in a variety of doses. Both calcium citrate and calcium carbonate are highly bioavailable sources compared with calcium gluconate. Calcium carbonate is cheaper, but may be less readily absorbed when taken between meals (11–13). Calcium citrate bioavailability is not affected by meals, but this has to be weighed against its higher cost and a content of almost 50% less calcium by weight (10); more or larger pills would be needed to deliver doses comparable to calcium carbonate, potentially reducing acceptability and adherence. Balancing all of these considerations, calcium carbonate is likely to be the most cost-effective choice in most settings.

Dosage of Calcium Supplements

Pregnancy is a state of high calcium demand, because ~30 g of calcium is transferred to the fetus during gestation (14). Bone turnover and intestinal calcium absorption increase markedly in support of fetal calcium demands, and numerous hormonal alterations occur to support calcium homeostasis across pregnancy (14). Therefore, the recommended dietary intake of calcium during pregnancy is similar to that of nonpregnant women of the same age (15).

The WHO-recommended daily dosage of calcium, 1.5–2.0 g elemental calcium/d, is higher than both the US estimated average requirement and the recommended dietary allowance for pregnant women (800 and 1000 mg, respectively) (15). The dosage recommended by the WHO is based on the range of dosages that have been tested in the most relevant and highest-quality trials, and at these dosages, the WHO guideline group considered the benefits to clearly outweigh the potential harms (1). This dosage range, however, should not be interpreted as either the minimal effective dosage or the optimal dosage, because no trials to date have specifically examined dosing strategies. Meta-analyses of lower-dose regimens have suggested comparable benefits to the WHO-recommended dosages (16); however, many of those trials were of lesser relevance or quality.

Calcium dose influences the percentage absorbed; as the calcium content of the dose increases, the fractional absorption of calcium decreases. Doses of ≤500 mg per administration are recommended (15). This implies that the WHO recommendations will involve ≥3 pill-taking events daily. Research on other drugs and supplements has found that adherence decreases as the number of pill-taking events increases (17).

Although research programs seek to establish the optimal supplementation dose, policymakers and program planners should seriously consider lowering the daily total calcium dosage to 1.0 g elemental calcium/d in current supplementation programs. This dosage would suffice to meet the estimated required intake of calcium during pregnancy with typical average dietary intake in low-income countries, reduce the logistical implications of shipping and inventory management associated with large supplement quantities, facilitate the training of health professionals, and enhance adherence by pregnant women. It is likely that the benefits of a feasible lower-dose regimen may be greater than a higher-dose regimen with low uptake and adherence (16).

Combining Calcium with Other Micronutrient Regimens

IFA supplementation as a part of routine antenatal care has long been recommended to improve maternal and neonatal outcomes, also based on a substantial body of evidence (18). Most health systems moving to adopt the new calcium recommendation already have a policy to provide IFA. Aligning and integrating both interventions could lessen the logistical complexities of adding a new intervention. It is essential to evaluate whether biological, epidemiologic, or behavioral considerations dictate otherwise.

Calcium has been reported to interfere with iron absorption in in vitro and short-term studies (19). However, over longer periods, the clinical effects of the interaction is minimal, because short-term interaction may be overcome by adaptive responses in iron regulatory mechanisms (20). The WHO suggested calcium regimen calls for ≥3 daily doses if kept to 500 mg elemental calcium/dose. Separation of calcium and IFA supplements would necessitate at least 4 separate administrations per day, increasing complexity with a possible negative impact on both calcium and IFA supplement adherence. On balance, the magnitude of the benefit of separating calcium from IFA is unknown, but would likely be outweighed by the impact of dosing complexity on adherence. Thus, we suggest that counseling messages for taking calcium and IFA pills be integrated so that women take IFA along with one of the calcium doses, either in the morning or the evening.

Timing of Supplementation during Pregnancy

The WHO recommends that calcium supplementation be initiated at a gestational age of 20 wk, based on the reference timing used in the meta-analyses on which the guidelines are based (1). This does not necessarily represent a clinically optimal time point, because the studies reviewed did not explore the effects of differential timing on outcomes (21).

Pragmatically, initiation of supplementation at the first antenatal care visit would allow synchrony of calcium and iron supplementation, because iron supplementation is recommended to begin as soon as possible in pregnancy. Implementation of the calcium supplementation recommendations is likely to be delivered through focused antenatal care (FANC) platforms in several settings (22). The second FANC visit typically occurs later than 24 wk of gestation, even when attendance is regular and on schedule. Whether delivered through FANC or by lay health workers (23), starting both supplements at first contact with the health system, even when earlier than a gestational age of 20 wk, would reduce the complexity, confusion, and possible delays that might arise with 2 different supplementation protocols. Also, women in many low-income settings present for initial antenatal care services very late in pregnancy, beyond week 20 of gestation. This should not preclude provision of calcium supplements, along with iron supplements. The mechanism of action of calcium supplementation is postulated to involve modulation of both placental vascularization and systemic vasomotor activity. Although these postulations are yet to be directly tested, this suggests that periconceptional calcium supplementation might be more beneficial, and initiation of supplementation beyond 20 wk of gestation, when inevitable, will still be useful. There are ongoing studies examining the clinical impact of initiating supplementation in the periconceptional period (24).

Side Effects of Calcium Supplementation

Calcium supplementation increased the risk of hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome in 2 studies (1, 24). HELLP syndrome is a rare, life-threatening obstetric complication; however, extremely few number of cases were reported in these studies. Calcium supplementation is also associated with postnatal bone resorption in Gambian women, which persists through subsequent lactation (25), but it is difficult to draw conclusions from a finding contrary to the hypothesis in a secondary analysis. The implication of this finding for bone health later in life remains unknown. It is also not known whether either of these side effects is dose-dependent; therefore, dose recommendations cannot be based on these effects. High doses of calcium have been reported to increase cardiovascular disease risk compared with lower doses (26). The validity of this finding is still questionable, because it is based on a set of studies limited by multiple testing. It is useful to continue to investigate potential modifications that might mitigate these side effects, including timing, dosage, salt type, and coadministration with other supplements. When balancing the magnitude and severity of known risk with the benefit of supplementation, however, consideration of these side effects should not impede initiation of policies and programs.

Conclusions

As reproductive health and nutrition programs seek to implement the WHO recommendations on calcium supplementation for the prevention of preeclampsia, further research is warranted to clarify issues related to minimum effective dose, timing of initiation, and mode of administration of prenatal supplements. Research to understand barriers and factors that will facilitate acceptability, adherence, and feasibility of full-scale implementation is urgently needed. Further research should also examine side effects and mitigating measures more rigorously.

In our view, while awaiting further research, policymakers and program planners should consider dosages of 1.0–1.5 g elemental Ca/d, depending on the local average for and variation in dietary calcium intake, logistical feasibility, and acceptability in the target population. Prudent practice would entail daily administration as calcium carbonate administered in divided doses of ≤500 mg elemental calcium per dose. For ease of prescribing and adherence, calcium (as with IFA) should be administered routinely to pregnant women from the earliest contact in pregnancy until delivery. The acute inhibitory effect of calcium on iron absorption translates to minimal effects in

clinical studies. Therefore, to simplify the regimen and facilitate adherence, providers should not counsel that calcium and IFA pills be taken separately. Calcium is associated with side effects, but the benefits of supplementation outweigh the risks. Limited data on habitual calcium intake in populations should not impede the implementation of these recommendations, which have the potential to substantially prevent maternal and perinatal morbidity and mortality. Preeclampsia is prevalent globally, and prenatal calcium supplementation should be considered in all low-income country settings, unless local data indicate that dietary calcium intake is already adequate. Beneficial programs and policies can be initiated with currently available information and revised as we continue to learn what works to benefit the health and survival of both women and infants.

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