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Calcium supplementation for the prevention of hypertensive disorders of pregnancy: current evidence and programmatic considerations

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Most low- and middle-income countries present suboptimal intakes of calcium during pregnancy and high rates of mortality due to maternal hypertensive disorders. Calcium supplementation during pregnancy is known to reduce the risk of these disorders and associated complications, including preeclampsia, maternal morbidity, and preterm birth, and is, therefore, a recommended intervention for pregnant women in populations with low dietary calcium intake (e.g., where ≥25% of individuals in the population have intakes less than 800 mg calcium/day). However, this intervention is not widely implemented in part due to cost and logistical issues related to the large dose and burdensome dosing schedule (three to four 500-mg doses/day). WHO recommends 1.5–2 g/day but limited evidence suggests that less than 1 g/day may be sufficient and ongoing trials with low-dose calcium supplementation (500 mg/day) may point a path toward simplifying supplementation regimens. Calcium carbonate is likely to be the most cost-effective choice, and it is not necessary to counsel women to take calcium supplements separately from iron-containing supplements. In populations at highest risk for preeclampsia, a combination of calcium supplementation and food-based approaches, such as food fortification with calcium, may be required to improve calcium intakes before pregnancy and in early gestation.

Keywords: calcium deficiency; calcium supplementation; hypertensive disorders; preeclampsia; pregnancy

Purpose

In March and April 2021, the Nutrition Science Program of the New York Academy of Sciences, in partnership with the Children's Investment Fund Foundation, convened a Calcium Task Force and hosted two virtual meetings. This Task Force is composed of experts in micronutrients,

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malnutrition, pediatrics, gynecology and obstetrics, biochemistry, public health, supplementation, and food fortification. During these two virtual meetings, the task force assessed the evidence on global calcium deficiency and its health consequences, and useful indicators of calcium absorption and intake. It also considered potential interventions, such as calcium supplementation for pregnant women to improve pregnancy outcomes and associated implementation challenges, as well as food-based interventions to improve the intake of this vital micronutrient, especially in populations with low calcium intake. The group was also commissioned to identify the research gaps and provide guidance for interventions and policies based on the most current available evidence. The following paper, as a consensus viewpoint, describes the task force's discussions and conclusions with regard to calcium supplementation for the prevention of hypertensive disorders of pregnancy, with a major focus on preeclampsia.

Although we have not conducted systematic reviews, the Calcium Task Force identified the relevant literature, critically appraised and discussed the evidence, and generated a group consensus.

Overview of requirements and inadequate intakes in pregnancy

Calcium is an essential mineral required for several vital functions in the human body, including skeletal, cardiovascular, neurological, muscular, hormonal, and enzymatic functions. Ninety-nine percent of calcium in the body is in the skeletal system (providing the rigidity and structure of bones), with the remaining 1% distributed between intra- and extracellular fluids; this is where calcium is involved in the majority of the metabolic processes, as well as in muscle contraction, nervous system transmission, enzymatic activation, and hormonal function. The primary long-term consequences of inadequate calcium intake include the development of rickets in children and osteopenia and osteoporosis in adults, thereby increasing the risk of osteoporotic bone fractures (especially in older individuals).[1,2]

During pregnancy, the skeleton of a full-term infant assimilates an estimated 30 g of calcium, a demand that is met largely by increased maternal intestinal calcium absorption, the rate of which more than doubles from early pregnancy to late pregnancy. Conversely, during lactation, maternal skeletal calcium resorption is the primary mechanism by which calcium is supplied to the infant via breast milk.[3]

Dietary reference values for calcium vary by age group and stage of the life course but most guidelines recommend an intake between 800 and 1300 mg of calcium for individuals 19 years of age and older.[1] While some guidelines recommend increased intake of calcium during pregnancy, other guidelines state that the metabolic adaptations during pregnancy (and lactation) compensate for the required calcium demand by the fetus (and for lactation).[4] Guidelines from Europe, FAO/WHO, the United States, and Canada recommend that pregnant women consume 1000–1300 mg of calcium/day,[4,5] without exceeding the upper limit of 2500 or 3000 mg/day (for pregnant/lactating women aged 19–50 years or 14–18 years, respectively).[5]

Globally in 2011, it was estimated that 3.5 billion people were at risk of calcium deficiency due to inadequate dietary supply, and approximately 90% of those at risk of deficiency were in Africa and Asia.[6] A recent systematic review that assessed dietary calcium intake during pregnancy worldwide showed that the mean calcium intake was 950 mg/day (95% confidence interval (CI): 870–1020 mg/day) for high-income countries and 650 mg/day (95% CI: 570–730 mg/day) for low- and middle-income countries (LMICs). Average calcium intakes below 800 mg/day were reported in at least 27% of high-income countries and in 88% of LMICs of the countries studied.[7]

Hypertensive disorders of pregnancy

Definition and etiology

Hypertensive disorders of pregnancy include preeclampsia and eclampsia, gestational hypertension (occurring after 20 weeks of gestation), and chronic hypertension (onset before pregnancy or, if first detected during pregnancy, then prior to 20 weeks of gestation).[8,9] Preeclampsia is a complex multiorgan disease defined as hypertension (systolic blood pressure at $\geq$140 mmHg and/or diastolic blood pressure at $\geq$90 mmHg, on at least two occasions 4 h apart) in a woman without prior hypertension, accompanied by the onset of at least one of the following new conditions at or after 20 weeks' gestation: proteinuria (e.g., $>$0.3 g/24 h), evidence of severe features manifesting as other maternal

organ dysfunction (e.g., thrombocytopenia, renal insufficiency, impaired liver function, neurological complications, such as visual symptoms, and headaches) or uteroplacental dysfunction (e.g., fetal growth restriction and stillbirth).[9–11] Superimposed preeclampsia on chronic hypertension is defined as the development of any of the above maternal organ dysfunctions in women with chronic hypertension or in the absence of pre-existing proteinuria.[10] Eclampsia is the development of seizures in the context of preexisting preeclampsia and is a life-threatening emergency that can occur during pregnancy or the postpartum period.[9]

Although not fully understood, the pathogenesis of preeclampsia is associated with early disturbances in placentation followed by generalized inflammation and progressive endothelial damage,[12–14] leading to hypertension. Preeclampsia can be further classified into preterm preeclampsia (with delivery before 37 weeks of gestation) or term preeclampsia (with delivery at or after 37 weeks of gestation). It is generally recommended that women with preeclampsia without severe features have a planned delivery at 37 weeks' gestation;[15] however, when severe features are present, an earlier delivery may be indicated.[9] Effective clinical management of women with hypertensive disorders depends on a balance of the benefits to the fetus of achieving maturation *in utero* versus the risks to the mother and fetus from prolonging the pregnancy.[10]

Maternal characteristics associated with an increased risk of preeclampsia are numerous, including: maternal age $\geq$35 years of age, adolescence, nulliparity, previous personal or family history of preeclampsia, short and long interpregnancy intervals, use of assisted reproductive technologies, obesity, Afro-Caribbean and South Asian origin, and comorbid medical conditions (including hyperglycemia in pregnancy, preexisting chronic hypertension, renal disease, and autoimmune disease).[10] Women with low calcium intake (e.g., $<$800 mg/day)[10] are also considered at increased risk of preeclampsia.

Prevalence and consequences

Hypertensive disorders during pregnancy (including preeclampsia) can have serious health consequences, such as acute morbidity, long-term disability, and the death of mothers and newborns.[12] In fact, they are among the leading causes of maternal death worldwide, accounting for approximately 29,000 maternal deaths per year.[16,17] According to the Global Burden of Disease, higher rates of mortality from maternal hypertensive disorders are observed in LMICs (Fig. 1).[18] In Africa and Asia, nearly one tenth of all maternal deaths are associated with hypertensive disorders of pregnancy, whereas one quarter of maternal deaths in Latin America have been associated with those complications.[12,19] In addition, a recent study on long-term consequences of hypertensive disorders of pregnancy showed that either gestational hypertension or preeclampsia was associated with an increased risk of premature mortality (before the age of 70 years), particularly from cardiovascular disease, regardless of the subsequent development of chronic hypertension.[20] While rates of maternal mortality fell significantly from 1990 to 2017, the largest reductions were observed in causes of death related to maternal hemorrhages (70% reduction), sepsis and other maternal infections (45%), and abortion and miscarriages (33%), but relatively little progress was observed in deaths due to hypertensive disorders of pregnancy (18%).[21]

Nonetheless, the majority of deaths related to hypertensive disorders during pregnancy can be avoided with timely and effective antenatal care.[12] The following sections will describe interventions to prevent hypertensive disorders of pregnancy, such as preeclampsia, and highlight the role of calcium supplementation during pregnancy on this and other maternal and fetal outcomes.

Interventions for prevention of preeclampsia: calcium and aspirin

Calcium. The observation that Mayan women in Guatemala had a low incidence of hypertensive disorders of pregnancy and high calcium intake led to the hypothesis that calcium intake could play a role in the development of preeclampsia.[22] Despite the low access to dairy products, these women were found to have a high calcium intake due to the Mayan practice of soaking corn, their staple food, in lime (calcium hydroxide) water before milling, resulting in corn with a high calcium content. Further basic and clinical studies confirmed this hypothesis.[23–25] Following these studies, WHO in 2011 recommended that all pregnant women from areas of low dietary calcium intake receive calcium

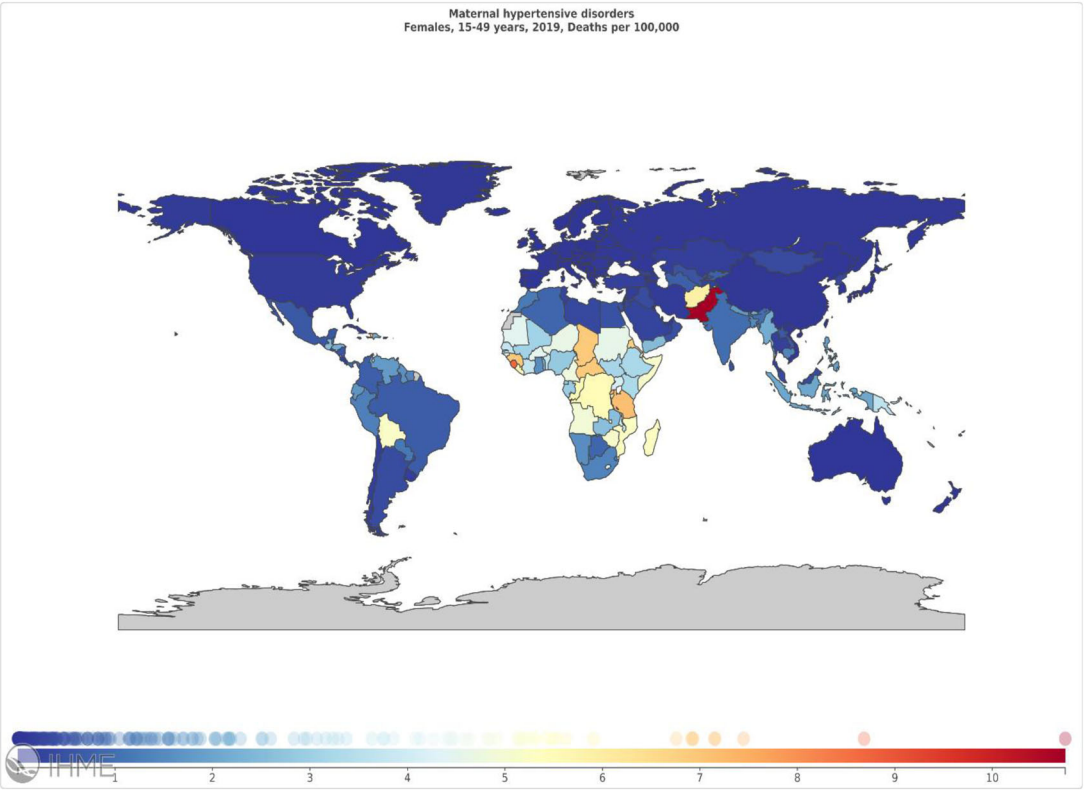

Figure 1. **Global rates of mortality due to maternal hypertensive disorders in 2019 (deaths/100,000), according to the Global Burden of Disease.[18] Pakistan presented the highest rate of 10.75 deaths due to maternal hypertensive disorders in each 100,000 women between 15 and 49 years of age.**

supplementation (1.5–2 g/day), as this is associated with a significant reduction of the risk (by at least 50%) of preeclampsia. More details about the global guidelines and supporting evidence can be found below. The WHO has updated the evidence in 2020, stating that "pre-pregnancy calcium supplementation for the prevention of pre-eclampsia and its complications is recommended only in the context of rigorous research," as a recent study suggests that prepregnancy low-dose calcium supplementation (500 mg/day) benefited women with a history of preeclampsia.[26]

For other nutrients, such as vitamin D, folic acid, and n-3 fatty acids (supplementation), as well as sodium intake reduction, there is limited evidence of their role in the prevention of preeclampsia.[27–29]

Aspirin. There is significant evidence that daily low-dose aspirin (75–300 mg) can reduce the risk of preeclampsia, given its ability to induce anti-inflammatory and proresolving lipid-derived mediators,[30] although the optimal dose remains unclear. The effect size varies among clinical trials due to differences in the timing of initiation of aspirin therapy (early pregnancy versus later) and dose. A recent meta-analysis showed a 70% reduction in preterm preeclampsia when aspirin was initiated at or before the 16th week of gestation and at a daily dose of ≥100 mg.[31] Guidelines from FIGO,[10] as well as the American College of Obstetrics and Gynecology,[32] recommend a daily dose of 150 and 81 mg, respectively (although this value could vary between 100 and 300 mg depending on maternal weight, as 2.5–3.5 mg/kg is suggested to inhibit platelet aggregation, with slight inhibition of prostaglandin production) and only for women identified at high risk[a] for preeclampsia. This is

[a]A woman is considered high risk when the risk is 1 in 100 based on the first-trimester combined test with maternal risk factors, measurements of mean arterial pressure,

Table 1. Studies assessing the effect of prenatal calcium supplementation on postpartum maternal bone health

Study (author, year)	Population (country, number of women, baseline calcium intake, % nulliparity, and mean age)	Intervention (amount and duration)	Follow-up period (and proportion of women breastfeeding)	Outcomes of intervention group
Studies demonstrating improved or no differences on bone health with calcium supplementation				
Diogenes *et al.* (2013)[34] and (2021)[35]	Brazil; 56 pregnant adolescents; ∼600 mg calcium/day; 100% nulliparous; and 17 years old	600 mg calcium and 200 IU vitamin D_3/day from 26 weeks until end of pregnancy	5 weeks (100%) and 20 weeks postpartum (77%/86%) Follow-up study: 56 weeks (50%)	Higher lumbar spine bone area at 5 weeks. Higher bone mineral content/area/density at lumbar spine and reduced rate of femoral neck bone loss at 20 weeks, but no significant differences between groups at 56 weeks.
Cullers *et al.* (2019)[33]	The United States; 64 pregnant women (21 African American; 20 Caucasian; and 23 other race/ethnicity); ∼733 mg calcium/day; 50% nulliparous; and 31 years old in intervention and 28 years old in control	1 g calcium/day from 16 weeks until end of pregnancy	4 and 12 months postpartum (mean duration of breastfeeding: 5.9 months)	Significant greater increases from baseline to 12 months in radial total and tibial cortical bone mineral density. Trabecular and total bone mineral density at the tibia trended toward greater gains from baseline to 12 months ($P < 0.06$).
Studies demonstrating negative bone health outcomes with calcium supplementation				
Jarjou *et al.* (2010)[38] and (2013)[39]	The Gambia; 125 pregnant women; ∼350 mg calcium/day; 16% nulliparous; and 27 years old	1.5 g calcium/day, from 20 weeks until end of pregnancy	12 months postpartum (100%) Follow-up study: 5 years (0%)	Lower bone mineral content/area/density at the hip; greater decreases in bone mineral at lumbar spine and distal radius during lactation. Lower bone mineral content and density at 5 years.

a higher dose than the 75 mg of aspirin recommended by WHO guidelines in 2011.[12] The aspirin regimen would ideally begin at 11–15 weeks of gestation and continue through 36 weeks or when delivery occurs, or when preeclampsia is diagnosed. To increase compliance, counseling patients on the risks of preeclampsia and benefits of prevention, as well as normalizing common aspirin side effects, is also recommended.

Calcium supplementation outcomes beyond preeclampsia

Benefits and risks of calcium supplementation on bone health

Only a few studies have assessed the effect of prenatal calcium supplementation (discontinued at the end of the pregnancy) on postpartum maternal bone health (Table 1). Two of these studies were conducted in the United States and Brazil in subpopulations with relatively low calcium intakes (600–733 mg/day). Both studies showed that prenatal calcium supplementation (600 mg/day–1 g/day) resulted in reduced postpartum bone resorption and improved bone recovery up to 12[33] and 20 weeks postpartum,[34] or found no significant differences in bone changes in longer follow-ups, at 56 weeks postpartum.[35]

Other studies conducted in populations of pregnant women with very low or adequate calcium intakes that extended calcium supplementation beyond pregnancy have reported equally positive

serum placental growth factor, and uterine artery pulsatility index.[10]

effects on bone health. In one trial comparing usual diet (group 1, control) with milk (group 2) and milk in combination with calcium supplements (group 3, providing 350 and 600 mg/day of calcium, respectively) were given to 36 Chinese women, with an average baseline intake of 480 mg/day, from 20 weeks of gestation to 6 weeks postpartum. At the end of the trial, bone mineral density values in the spine and whole body were higher in women who received milk and calcium supplementation (groups 2 and 3), when compared with the usual diet group (group 1).[36] Another study conducted in Mexico, involving 670 pregnant women with a baseline intake of calcium of 1100 mg/day, provided supplementation with 1200 mg/day of calcium from the first trimester until early postpartum (i.e., 1 month after giving birth).[37] The results showed reduced bone resorption during pregnancy and at 1 month postpartum (while still receiving the calcium supplement), and these effects were stronger with increased compliance. However, longer-term follow-up has not been reported, so it is unknown if the benefits were sustained after discontinuing calcium supplementation.

In contrast with the abovementioned studies, a trial of calcium supplementation in rural Gambian women with very low calcium intake (average 350 mg/day) found a negative effect on bone health (Table 1).[38] This study was composed of a subset of 125 participants from a larger trial of calcium supplementation and blood pressure during pregnancy. Participants who were randomized to 1.5 g calcium/day from 20 weeks until end of pregnancy had significantly lower maternal bone mineral content and bone area and bone mineral density at the hip throughout 12 months of lactation, compared with women randomized to placebo. Women who received calcium supplementation until delivery also experienced greater decreases in bone mineral content/area/density during lactation at the lumbar spine and distal radius and had biochemical changes consistent with higher levels of bone mineral mobilization. The study authors hypothesized that calcium supplementation disrupted the processes of calcium conservation and adaption to the local low calcium diet previously observed in this population.[38] A follow-up study after approximately 5 years showed that the lower bone mineral content and density of the supplemented group remained long-term when the women were not pregnant and had not lactated for at least 3 months.[39] However, it should be noted that this study excluded women with an underlying condition, including those at higher risk of developing preeclampsia, and the results of this subset study have not been replicated in other populations.

The negative effects of prenatal calcium supplementation on maternal bone health found in the Gambian study have not been reproduced in other populations with low calcium intakes provided during pregnancy[33–35] or continued during lactation,[36,37] although longer follow-up periods would be required to draw firmer conclusions. If the adverse bone health effects were replicated in other studies, they would need to be weighed against the benefits of the well-documented reduction of preeclampsia, which is a potentially life-threatening condition. It should also be noted that the study conducted in Gambian women used a higher dose of calcium supplementation when compared to the other studies (1.5 g[38] versus 0.6 g[34] to 1 g[33]), and it remains unknown whether continued calcium supplementation through lactation would have mitigated the observed negative effects on maternal bone health.

A recent systematic review of trials providing calcium supplementation to lactating women for the improvement of bone density identified five studies with a total of 567 participants, but the low quality of these studies (e.g., small, high risk of bias, and lack of assessment of baseline calcium intake) or the characteristics of the study populations (e.g., adequate dietary calcium intake before supplementation) prevented the authors from drawing conclusions about the effects of calcium supplementation during lactation.[40]

Other outcomes of calcium supplementation

In addition to a reduction in the risk of preeclampsia, prenatal supplementation with high-dose calcium (≥1 g/day) has been found in pooled analyses to reduce the prevalence of gestational hypertension (35% risk reduction, 95% CI: 19–47%), serious maternal morbidity or death (20% risk reduction, 95% CI: 8–34%), and preterm birth (24% risk reduction, 95% CI: 3–40%).[41]

There is also a potential benefit for decreased systolic blood pressure among children whose mothers were supplemented during pregnancy.[42,43]

One follow-up study reported a decrease in the incidence of dental caries in childhood following maternal calcium supplementation during pregnancy.[44] However, the finding has not been confirmed, since children's dental outcomes have not been reported from other maternal calcium supplementation trials.[45]

Little evidence exists to support a benefit of calcium in reducing fetal outcomes, such as neonatal death and stillbirth, neonatal intensive care unit admission, growth restriction, low birth weight, or small for gestational age, as well as maternal complications, including placental abruption, intensive care unit admission, and cesarean birth.[41]

One follow-up study from the Gambia trial discussed above[38] suggested that calcium supplementation of pregnant women with low calcium intakes could result in slower growth among female children compared with placebo and accelerated growth among males by age 8–12 years.[46] However, there are no other studies that have confirmed this finding. Overall, either a lack of data or conflicting results prohibits a determination on whether maternal calcium supplementation can reduce postneonatal mortality, growth faltering, incidence of malnutrition, developmental delay, or metabolic derangement in the offspring, or maternal or child bone loss.[45,47] The impact of supplementary calcium alone or with vitamin D during pregnancy on maternal and offspring bone health is an area that requires further research.

Guidelines and supporting evidence on calcium supplementation before and during pregnancy to prevent preeclampsia

Between 2011 and 2020, the WHO published and updated several guidelines that included recommendations on prenatal calcium supplementation for the prevention of preeclampsia and its complications. Table 2 summarizes the changes in recommendations and supporting evidence over time. The number of studies available for assessment increased over the years and consistently supported the recommendation to provide daily calcium supplementation to pregnant women with low dietary calcium intake to reduce the risk of preeclampsia. While the 2011 and 2013 guidelines recommend calcium supplementation particularly among those at higher risk of developing preeclampsia or hypertension, the most recent guidelines (2016 and 2018) recommend this intervention for all pregnant women in areas where dietary calcium intake is low, independent of the individual-level risk of preeclampsia or hypertension. Recent evidence also suggests a potential benefit of initiating calcium supplementation before pregnancy[26] for the prevention of this same outcome. A 2019 multicountry trial[26] ($n = 1355$) compared 500 mg calcium or placebo daily from enrollment before pregnancy until 20 weeks of gestation, followed by 1.5 g of calcium/day after 20 weeks of gestation in both intervention and placebo groups. Although the intervention did not result in an overall statistically significant reduction of preeclampsia, the effect was statistically significant (relative risk (RR) for preeclampsia = 0.66, 95% CI: 0.44–0.98; $P = 0.037$) among participants with compliance of more than 80% from the last prepregnancy visit until 20 weeks of gestation. This study was the basis for the most recent WHO guideline (2020)[48] recommending calcium supplementation in the prepregnancy period in the context of rigorous research.

It is noteworthy that the 2018 Cochrane Review[49] and WHO guidelines[50] reported that prenatal calcium supplementation of women in areas of low calcium intake also significantly reduces maternal death or serious morbidity by 20%. With regard to the benefits observed in the reduction of preterm birth, the guideline development group agreed that the effect of calcium on preterm birth is probably not distinct from the effect on preventing preeclampsia, because preterm birth is frequently a consequence of preeclampsia.[50] Further research is needed to elucidate the mechanism through which calcium supplementation reduces preterm birth, whether indicated or spontaneous. Results of the largest multicountry antenatal calcium trial suggested that effects were predominantly seen for indicated rather than spontaneous preterm birth.[51]

Potential nutrient interactions and side effects of prenatal calcium supplementation

Review of calcium–iron and calcium–zinc interactions

Single-meal studies show that calcium intake can interfere with the absorption of iron and zinc.[52,53] While these short-term studies suggest that calcium supplements inhibit iron absorption by 28–55%, long-term studies (6 months to 4 years) showed no

Table 2. World Health Organization (WHO) recommendations on prenatal calcium supplementation for the prevention of preeclampsia since 2011

Guideline, year of publication	Recommendation	Supporting evidence: outcomes related to calcium supplementation
WHO recommendations for prevention and treatment of preeclampsia and eclampsia (2011)[12]	"In areas where dietary calcium intake is low, calcium supplementation during pregnancy (at doses of 1.5−2.0 g elemental calcium/day) is recommended for the prevention of preeclampsia in all women, but especially those at high risk of developing preeclampsia" (moderate quality, strong recommendation).	Cochrane review (2010)[77] on prenatal calcium supplementation for preventing hypertensive disorders Preeclampsia RR (95% CI): – overall: 0.45 (0.31−0.65) *(13 trials, 15,730 women)* – low-risk women[a]: 0.59 (0.41−0.83) *(8 trials, 15,143 women)* – high-risk women: 0.22 (0.12−0.42) *(5 trials, 587 women)* – low calcium intake: 0.36 (0.20−0.65) *(8 trials, 10,678 women)* – adequate calcium intake: 0.62 (0.32−1.20) *(4 trials, 5022 women)* Serious morbidity RR (95% CI): 0.80 (0.65−0.97) *(4 trials, 9732 women)* Other outcomes (e.g., eclampsia): NS
WHO guideline: calcium supplementation in pregnant women (2013)[78]	"In populations where calcium intake is low, calcium supplementation as part of the antenatal care is recommended for the prevention of preeclampsia in pregnant women, particularly among those at higher risk of developing hypertension" (strong recommendation).	Same as 2011 guideline above
WHO recommendations on antenatal care for a positive pregnancy experience (2016)[61]	"In populations with low dietary calcium intake, daily calcium supplementation (1.5−2.0 g oral elemental calcium) is recommended for pregnant women to reduce the risk of preeclampsia" (context-specific recommendation)	Cochrane review (2014),[79] an update of a prior review (2010)[77] Cochrane review (2015)[62] of calcium supplementation for improving other pregnancy and infant outcomes Preeclampsia RR (95% CI): same as above Serious morbidity RR: same as above Other additional maternal and fetal outcomes: NS Preterm birth RR (95% CI) for trials with high dose of calcium (≥1 g/day): 0.81 (0.66−0.99) *(12 trials, 15,479 women)*[b]
WHO recommendation: calcium supplementation during pregnancy for the prevention of preeclampsia and its complications (2018)[50]	"In populations with low dietary calcium intake, daily calcium supplementation (1.5−2.0 g oral elemental calcium) is recommended for pregnant women to reduce the risk of preeclampsia" (context-specific recommendation, moderate-certainty evidence)	Cochrane review (2018),[49] an update of a prior review (2014)[79] High-dose (≥1 g/day) versus placebo *(same trials and effect estimates as Cochrane review (2010)[77])* Preeclampsia RR (95% CI): – all women: 0.45 (0.31−0.65) – low-risk women: 0.59 (0.41−0.83) – high-risk women: 0.22 (0.12−0.42) – low calcium intake: 0.36 (0.20−0.65) – adequate calcium intake: NS Preterm birth RR (95% CI): 0.76 (0.60−0.97) *(11 trials, 15,275 women)* Maternal death or serious morbidity if low calcium intake RR (95% CI): 0.80 (0.66−0.98) *(4 trials, 9732 women)* Other outcomes: NS Low-dose (<1 g/day, started at 20 − 22 weeks of gestation) versus placebo or no treatment Preeclampsia RR (95% CI): 0.37 (0.23−0.60) *(3 trials, 812 women)* High blood pressure RR (95% CI): 0.60 (0.40−0.91) *(2 trials, 390 women)* Neonatal intensive care unit admission RR (95% CI): 0.44 (0.20−0.99) *(1 study, 422 infants)* Perinatal death: very low certainty Preterm birth RR (95% CI): 0.40 (0.21−0.75) *(1 study, 422 women)* High dose (≥1 g) versus low dose (<1 g) – Preeclampsia: RR (95% CI): 0.42, 95% CI 0.18−0.96 *(one study, 262 women)* – Eclampsia and stillbirth: very low certainty
WHO recommendation: calcium supplementation before pregnancy for the prevention of preeclampsia and its complications (2020)[48]	"Pre-pregnancy calcium supplementation for the prevention of preeclampsia and its complications is recommended only in the context of rigorous research" (recommendation in research context)	Cochrane review (2019)[24] and multicenter trial (2019)[26] 500 mg/day from before pregnancy until 20 weeks of gestation followed by 1.5 g/day for the remainder of pregnancy resulted in: Preeclampsia RR (95% CI): – all women: NS – compliance > 80%: 0.66 (0.44−0.98) – maternal death, eclampsia, severe preeclampsia, severe maternal morbidity: NS or very low certainty

[a] Women at high risk of developing preeclampsia were those having one or more of the following risk factors: previous preeclampsia, diabetes, chronic hypertension, renal disease, autoimmune disease, and multiple pregnancies.
[b] The guideline development group agreed that the effect of calcium on preterm birth is probably not distinct from the effect on preventing preeclampsia, as preterm birth is frequently a consequence of preeclampsia.
NS, nonsignificant.

effect of calcium supplementation (with levels of 500–1200 mg/day).[54] Minihane and Fairweather-Tait showed that one-time calcium supplementation at 400 mg in adults significantly reduced iron absorption in a single meal.[53] However, chronic calcium supplementation at 1200 mg/day over a period of 6 months did not decrease iron status, as there were no changes in any of the hematologic indexes (hemoglobin, hematocrit, zinc protoporphyrin, and plasma ferritin).[53] Similarly, calcium supplementation of 1 g/day provided to 354 adolescent premenarcheal women over a period of 4 years did not affect their iron status.[55] Iron absorption is known to be upregulated as stores decrease. A recent systematic review of calcium intake and iron status in human studies reported an inverse dose–response association of calcium intake with the serum ferritin concentration but no reduction in the hemoglobin concentration. The authors concluded that prescribing separation of calcium and iron supplements in free-living pregnant women is unlikely to affect the anemia burden.[56]

Another study conducted in adolescent women to determine the effect of long-term calcium supplementation (1 g/day) on zinc utilization (from a diet containing 6.3 mg/day of zinc) during a 14-day period found no significant differences in zinc balance, fecal zinc, urinary zinc, or net zinc absorption between the group that received calcium supplementation and the control group.[57]

Side effects and adverse outcomes

Side and adverse effects of calcium supplementation have been systematically investigated. A systematic review of 10 studies with more than 8000 patients with osteoporosis reported no significant increase in the risk of nephrolithiasis associated with calcium supplementation,[58] and new evidence suggests that a diet with adequate calcium intake ($\geq$1 g/day) may in fact prevent the formation of calcium stones in hypercalciuric stone–forming adults.[59] Another meta-analysis of 63,563 postmenopausal women showed that calcium supplementation, with or without vitamin D, has no effect on the overall risk of coronary heart disease (RR = 1.02, 95% CI: 0.96–1.09) or all-cause mortality risk (RR = 0.96, 95% CI: 0.91–1.02).[60] When the study authors analyzed the individual components of coronary heart disease, calcium supplementation had no effect on myocardial infarction (RR = 1.08, 95% CI, 0.92–1.26), angina pectoris and acute coronary syndrome (RR = 1.09, 95% CI: 0.95–1.24), or chronic coronary heart disease (RR = 0.92, 95% CI: 0.73–1.15).

With regard to pregnant women, the 2016 WHO guidelines[61,62] cited the limited evidence that suggests there are no increased risks of several potential adverse effects of prenatal calcium supplementation, including:

- headache, vomiting, backache, swelling, vaginal and urinary complaints, dyspepsia, and abdominal pain (1 trial with 8312 women; RR = 1.02, 95% CI: 0.93–1.12);
- urinary stones (3 trials with 13,419 women, RR = 1.11, 95% CI: 0.48–2.54);
- renal colic (1 trial with 8312 women; RR = 1.67, 95% CI: 0.40–6.99);
- impaired renal function (1 trial with 4589 women; RR = 0.91, 95% CI: 0.51–1.64); or
- gallstones (1 trial with 518 women; RR = 1.35, 95% CI: 0.48–3.85).[61]

However, it must be noted that the general reporting of adverse effects was inconsistent across published trials, such that most estimates related to potential harms were imprecise. Furthermore, there was an increased risk of hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome among women randomized to high-dose calcium supplementation (2 trials with 12,901 women, RR = 2.67, 95% CI: 1.05–6.82).[41] Nevertheless, the absolute number of events was low (2.5/1000 versus 0.9/1000), which is a limitation that should be outweighed by the overall reduction in death or severe morbidity associated with calcium supplementation.[41]

Challenges in implementing prenatal calcium supplementation guidelines and how can they be mitigated

Overview of implementation challenges

There are a number of challenges and barriers associated with the implementation of the existing guidelines on calcium supplementation during pregnancy for the prevention of preeclampsia,[50] such as:

Cost and supply/delivery challenges. The unitary cost of 600 mg calcium has been estimated to be \$0.0213 USD/tablet. Thus, 3 × 600 mg tablets per day for 20 weeks is estimated to cost \$8.95 USD

per pregnancy.[50] The weight and volume of the calcium supplements, which are bulky, can also have cost and logistical implications with respect to continuous supply, storage, and transport for health services.[50]

Concerns about impact on iron absorption. As described above, single-meal studies suggested potential negative interactions between iron and calcium supplements, but research on longer-term supplementation demonstrates that this is not a problem. Currently, WHO recommends that these two micronutrients should preferably be administered several hours apart rather than concomitantly,[61] meaning three to four calcium supplements plus one iron and folic acid supplement (IFA) taken at separate times daily. Women report that adhering to regimens that separate calcium and IFA supplements dosing is very challenging.[63,64] Thus, this recommendation is neither feasible and nor supported by research evidence.

Adherence and behavior change challenges. The suggested regimen for calcium supplementation is 1.5–2.0 g/day, with the total amount divided into three doses, preferably taken at mealtimes.[50] The percentage of calcium absorbed depends on the total amount of elemental calcium consumed at one time; as the amount increases, the percentage absorption decreases.[65] Absorption is highest in doses $\leq$500 mg; hence, the recommendation to split high daily doses of calcium into small doses of 500 mg consumed throughout the day.[2] Given that the prescribed number of doses per day is inversely related to compliance,[66] taking three tablets a day, in addition to IFA supplements, can lead to poor acceptability and adherence.

Recent studies showed that factors that hindered adherence to the recommended prenatal calcium supplementation often had little to do with calcium itself. Rather, women missed doses (particularly the midday doses) due to forgetting, working outside the home, or not having easy access to food or water at dosing times. Women were more likely to stop taking supplements altogether if family members were unsupportive, or if they feared being stigmatized, as in some countries taking multiple daily pills during pregnancy is associated with being HIV positive.[63,64]

Published implementation studies

A number of studies have assessed the feasibility of implementing calcium supplementation as an intervention to prevent preeclampsia/eclampsia in pregnant women.

A pilot study conducted in Dailekh, Nepal, showed that providing calcium supplements free of charge through antenatal care services and counseling by community health volunteers was feasible and effective, achieving a high coverage (94.6%) of pregnant women in the district. The full course of calcium (two tablets per day of 500 mg each, starting at 4 months of gestation for 5 months or until delivery) was provided to 82.3% of the women and consumed by 67.3% of all calcium recipients.[67] A small proportion of women (10%) stopped taking the calcium tablets before giving birth because they felt sick, experienced side effects, forgot to take the calcium supplement, found it inconvenient to take the supplements every day, or found it difficult to take the large-sized tablets.

In a small acceptability trial of calcium supplementation conducted in two rural districts of Ethiopia, pregnant women were randomly assigned to three regimens varying in dose and timing and were later given a choice of regimens.[64] The aim was to understand barriers and facilitators of adherence and determine whether simplified prenatal calcium supplementation regimens would be more acceptable than a complex regimen and result in adequate consumption. Women preferred 2-event regimens to 3- or 4-event regimens, but adherence did not differ significantly across regimens with 2 (81.1%), 3 (83.4%), or 4 (77.1%) pill-taking events. The authors concluded that despite women experiencing challenges with midday dosing and the stigma associated with pill-taking during pregnancy, high acceptability and adherence is feasible. However, they emphasized the critical importance of counseling to explain the purpose of supplementation and regimen details and the use of simple home-based reminders. Interpersonal counseling to enhance motivation, engage family members, and address key barriers was more effective than reducing dosage to improve adherence. The authors also observed that a regimen of three doses of calcium simplified to allow coconsumption with IFA resulted in over 80% of the women consuming 1000 mg or more daily.[64]

Table 3. Policy guidance of prenatal calcium supplementation for the prevention of preeclampsia

Question	Answer	Rationale/comments
Whom?	Pregnant women in populations with low dietary calcium intake (e.g., ≥25% of individuals in the population have intakes less than the 800 mg calcium/day[a])	No consensus definition for "low calcium intake" but evidence suggests <800 mg/day. Where habitual calcium intake is unknown, calcium supplements are likely beneficial[80]
What?	Calcium carbonate (≤500 mg of elemental calcium per dose)	Calcium carbonate is likely to be the most cost-effective choice. It is not necessary to counsel women to take calcium supplements separately from iron-containing supplements, given the minimal inhibitory effect of calcium on iron absorption and the likelihood of increased adherence when both supplements are taken at the same time[80]
How much?	WHO recommends 1.5−2 g/day;[50] limited evidence suggests that less than 1 g/day may be sufficient[81] (if resource constrained: 500 mg/day)	Limited evidence to date supports efficacy of less than 1000 mg/day (240−800 mg).[81] Giving 500 mg to three times the number of women is likely to have a much greater public health impact
When?	As early as possible in pregnancy	The underlying pathophysiology begins in the first half of pregnancy; supplementation starting in prepregnancy reduces diastolic blood pressure[26]
How?	Prenatal supplementation combined with food fortification	Staple food fortification may be the most feasible route to improving calcium intakes before pregnancy and in early gestation in the long term. Supplementation is required in the interim when intakes are low and may still be needed in those at risk (e.g., nonconsumers of fortified foods)

[a] Extrapolated from cutoffs of inadequate zinc intake proposed by the International Zinc Nutrition Consultative Group[82] and from the calcium Estimated Average Requirements proposed by the Institute of Medicine.[83]

Another study examined factors that influence calcium supplementation delivery and uptake of 32 pregnant women in Kenya.[63] It similarly showed that reminder materials and adherence partners (providing support to help with remembering to take the pills) improved adherence.[68,69] This study also recommended a consistent supply of supplements, high-quality counseling from antenatal care providers, reminder materials for women to take home, and family support for the successful integration of calcium supplementation into antenatal care.

The integration of calcium supplementation into primary healthcare (in conjunction with IFA supplementation) has also been tested in 16 facilities and 990 women in Kenya, which proved to be feasible. Healthcare providers were given job aids, trained in counseling techniques and supplementation guidelines, and pill-taking calendars were developed to promote behavior change in pregnant women. Surprisingly, supplementation regimens of 1.5 g of calcium (three pills) per day did not result in lower adherence when compared with lower-dose supplementation regimens of 1 g (two pills) of calcium per day.[70] As in the research reported above, social support for calcium supplementation was significantly associated with adherence, suggesting that family engagement may facilitate the implementation of this intervention.[71]

A nutrition-focused "Maternal, Neonatal, and Child Health" intervention that included interpersonal counseling in home visits and one-on-one antenatal care sessions was compared to a standard "Maternal, Neonatal, and Child Health" program in a cluster-randomized trial in Bangladesh. The more intensive program resulted in higher proportions of women attending early antenatal care visits and higher consumption of calcium and IFA tablets.[72] Additionally, engaging men in the interventions through counseling, husbands' forums, and videos increased husbands' relevant knowledge, attitudes, norms, self-efficacy, and support for their wives in the nutrition-focused intervention arm.[73] As a result, husbands' behavioral determinants and supportive activities were, in part, responsible for the

Table 4. Future research questions

1, In populations with low calcium intakes, what is the effect of prenatal calcium supplementation on the maternal bone health and other maternal and child health outcomes if continued during lactation?
2, What is the efficacy and safety of combining calcium with vitamin D supplementation? Does concomitant supplementation of calcium with vitamin D allow a lower calcium supplementation dose (to achieve the same benefits)?
3, What quantity of total calcium intake from diet and supplementation during pregnancy provides optimal effects on maternal and offspring outcomes?
4, What is the effect of prenatal calcium supplementation on the risk of spontaneous versus indicated preterm birth? By what mechanism does prenatal calcium affect the risk of severe maternal morbidity/mortality? To what degree are the underlying mechanisms shared across these clinical outcomes?
5, How can adult or adolescent women be reached periconceptionally to ensure adequate calcium intake? Which contextual factors are likely to influence intervention reach and coverage of women periconceptually?
6, How can adherence to multiple tablets (e.g., calcium supplements, IFA/multiple micronutrient supplements, and aspirin) be optimized in pregnant women?
7, How can supplement form (tablets, gummy, chewable, powders, etc.), packaging (bottles, labels, blister packs, etc.), and delivery methods (i.e., 180-day supply at first visit versus refills) support high adherence to calcium supplementation in pregnancy?
8, What is the cost effectiveness of calcium supplementation in the context of public health programs?

increased intake of calcium and IFA supplements. This reinforces the evidence above that adherence to calcium (and other antenatal supplements) is possible with well-designed and implemented strategies to communicate essential information and support women in overcoming obstacles to sustained supplementation.

Ongoing research to improve implementation: low-dose calcium supplementation

Current WHO recommendations suggest the utilization of high-dose calcium supplements (i.e., 1.5–2 g), usually implying 500 mg doses three to four times daily.[50] This recommendation was formulated based on the doses used in trials showing positive outcomes. However, research to define the minimum effective dose has not yet been done. This high dose with a thrice-daily dosing schedule may be a constraint to implementation of calcium supplementation in settings where it is deemed too costly and demanding.

There are two ongoing parallel, individually randomized, double-blind, noninferiority trials in India and Tanzania, testing high-dose (500 mg 3×/day) and low-dose (500 mg) calcium supplementation to prevent preeclampsia and preterm birth in nulliparous women at <20 weeks of gestation.[74] The trial in India will also provide 250 IU/day of vitamin D3 to both study groups; no vitamin D3 supplements will be given in Tanzania. The trials will follow the cohorts of 11,000 women each until 6 weeks postpartum and will also assess other outcomes, such as gestational hypertension, small for gestational age, and perinatal mortality. To further understand the mechanisms by which calcium acts on these outcomes, the team is collecting blood samples from a subset of trial participants, examining angiogenic and inflammatory markers, endocrine regulators, and metabolic mediators. The results of these studies may point a path toward simplifying supplementation regimens and lowering the amount of calcium needed in fortification programs aimed at providing adequate levels of calcium to pregnant women.

Policy recommendations for prenatal calcium supplementation based on evidence

Based on the existing evidence, the Calcium Task Force proposes the policy guidance shown in Table 3, including a "hierarchy of targets," for calcium supplementation during pregnancy for the prevention of preeclampsia.

Concomitant use of supplementation and fortification

Despite being efficacious, prenatal calcium supplementation requires regular access to the healthcare system to obtain the supplements, and many women in LMICs do not seek (early) antenatal care unless they have specific concerns. Women at high risk of preeclampsia often face barriers to obtaining antenatal care.[75] Furthermore, additional intake of calcium before pregnancy seems to be beneficial for women with a history of preeclampsia, although this has only been studied through supplementation.[26]

Calcium supplementation also does not solve the problem of a population that has a widespread problem of insufficient calcium intakes that may contribute to the presence of rickets or other adverse health outcomes, as well as preeclampsia in pregnant women. Thus, strategies to increase regular dietary intake of calcium in areas of low intake are needed. This can include dietary diversification if good, affordable, and acceptable food sources of calcium are available together with fortification (and/or other food processing techniques), if appropriate vehicles can be identified. The selection of the appropriate vehicle and dose of calcium to add to foods is discussed in another paper of this special issue.[76] Supplementation with calcium may still be required, particularly as fortification may take time to implement and for those who may be missed. If routine calcium intakes from fortified foods are increased, this may reduce the recommended dose of calcium supplementation for pregnant women.

Data gaps/future research

The task force identified several areas where more research is needed with regard to calcium supplementation during pregnancy, with a focus on strategies that may increase compliance or make programs more widely accessible. Table 4 lists several questions that remain unanswered and Appendix S1 (online only) includes the justification for each question.

Conclusion

Calcium supplementation during pregnancy can safely reduce the risk of maternal hypertensive disorders, including preeclampsia, as well as maternal morbidity and preterm birth. Addressing low calcium intakes in populations at highest risk for preeclampsia will likely require a combination of supplementation and food-based approaches including fortification. The WHO guidelines on maternal calcium supplementation are not widely implemented, at least in part due to cost and logistical issues related to the large dose and burdensome dosing schedule. Despite this, policymakers can consider evidence-based policy guidance to best deliver prenatal calcium supplementation to those who would benefit the most from this intervention.

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Supporting information

Additional supporting information may be found in the online version of this article.

Appendix S1. Justification of future research needs

Competing interests

The authors declare no competing interests.

Peer review

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