WORLD HEALTH ORGANIZATION
DEPARTMENT OF NUTRITION FOR HEALTH AND DEVELOPMENT
EVIDENCE AND PROGRAMME GUIDANCE UNIT

Calcium supplementation in pregnant women

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Table of contents

Acronyms and abbreviations

BNF	British National Formulary
CI	95 % Confidence Interval
EML	Essential Medicines List (for adults)
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
LMICs	Low and Middle-Income Countries
MHRA	Medicines and Healthcare products Regulatory Agency
MSH	Management Sciences for Health
NEML	National Essential Medicines List
RR	Relative Risk
SRA	Stringent Regulatory Authority
TGA	Therapeutic Goods Administration
UK	United Kingdom
USD	United States Dollar
WHO	World Health Organization

Executive summary

This application presents a comprehensive review of the evidence for daily supplementation with calcium in pregnant women to improve gestational and birth outcomes, particularly preterm delivery and the risk of gestational hypertensive disorders, including pre-eclampsia.

Two recent Cochrane systematic reviews investigated whether calcium supplements consumed on a daily basis during pregnancy safely improved maternal and infant outcomes. Calcium supplementation during pregnancy significantly reduced the risk of pre-eclampsia and high blood pressure (with or without proteinuria). There was no effect on eclampsia, maternal death or maternal admission to the intensive care unit. Although it is a rare adverse event, and likely a statistical artifact, women who received calcium supplements had a significantly higher risk of developing HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome, which is an obstetric complication of severe pre-eclampsia.

In regard to infant outcomes, there was no effect of calcium supplementation on preterm birth, although a subgroup analysis suggested that women who received 1.5 g of elemental calcium or more per day delivered fewer preterm babies than those women with a lower calcium intake. Calcium supplementation did not have a detectable effect on the risk of low birth weight, admissions to neonatal intensive care unit, stillbirths or neonatal death before hospital discharge.

Calcium is generally well tolerated. Some mild side-effects such as headache, constipation, laxative effect, acid rebound, nausea, vomiting, anorexia, abdominal pain, xerostomia (dry mouth) or flatulence may occur 1% to 10% of the time.

Availability analysis shows that most nations tend to have some form of calcium on their NEMLs, although there is variability in the chemical form used. Their strength may be addressed by listing a specific formulation on the WHO model formulary. Furthermore, the cost analysis shows that calcium carbonate salt is the most economical supplement. This salt contains the highest amount of elemental calcium content, thus the pill burden is lower with this formulation.

The recommendations for changes to the EML Section 27 – Vitamins and Minerals, are as follow:

1. Add 500 mg of elemental calcium in the form of calcium carbonate to the EML.
    a. Dose, frequency and duration: Take three (3) tablets three times a day preferably with meals, for the duration of the pregnancy to achieve daily intake of 1.5 grams of elemental calcium

I. Background and rationale for the application

This EML application will provide evidence for the use of calcium supplements in pregnant women for the prevention of gestational hypertensive disorders and preterm delivery as a public health measure to improve maternal and child health.

II. Background on calcium and gestation

Calcium is essential for many diverse processes in the body, including bone formation, muscle contraction, and enzyme and hormone functioning (*1*). Inadequate calcium consumption by pregnant women can lead to adverse effects in both the mother and the fetus and produce osteopenia, tremor, paraesthesia, muscle cramping, tetanus, delayed fetal growth, low birth weight, and poor fetal mineralization (*2*).

Calcium supplementation has shown to produce a beneficial effect in reducing the risk of pregnancy-induced hypertension (*2*), whereas studies evaluating the effect of supplementation on maternal bone mineral density and fetal mineralization have been less conclusive (*3*). Hypertensive disorders of pregnancy include (pre-existing) chronic hypertension and gestational hypertension, pre-eclampsia and eclampsia. Pre-eclampsia is diagnosed when gestational hypertension (maternal blood pressure $\geq$ 140/90 mmHg for the first time in the second half of pregnancy) is accompanied byproteinuria greater than 300 mg in a 24-hour period (*4*). Chronic hypertension may also be complicated by super-imposed pre-eclampsia. The pathogenesis of pre-eclampsia has not been thoroughly elucidated; however, it is related to disturbances in placentation in early pregnancy, followed by generalized inflammation and progressive endothelial damage (*4*).

Pre-eclampsia can be classified as mild or severe. In severe pre-eclampsia blood pressure is $\geq$ 160/110 mm Hg, there is proteinuria $\geq$ 2 g /24 h and/or substantial maternal organ damage is present (*4*). Such end organ damage as a result of preeclampsia can present with hemolysis, elevated liver enzymes and low platelet count, a constellation of symptoms known as HELLP syndrome (*4*). The progression from mild to severe pre-eclampsia can be rapid and unexpected and can result in maternal death. Development of eclampsia from pre-eclampsia can occur in 5-8% of the women and is characterized by new-onset generalized seizures (*4*, *5*).

Calcium in supplements may come in the form of carbonate, citrate, lactate or gluconate, and in general has good bioavailability. Supplements are inexpensive and readily accessible.

1. Public health relevance of pre-eclampsia and preterm birth

Poor maternal and newborn health and nutrition remain significant contributors to the burden of disease. Worldwide an estimated 287 000 women died in 2008 from pregnancy-related causes and 99% of these deaths occured in LMICs (*5*, *6*). Approximately 2.6 million babies were stillborn and 3.1 million babies died in the

first 28 days of life, mostly due to maternal health complications, preterm birth, low birth weight, severe infections and asphyxia (*6*).

Hypertensive disorders of pregnancy affect about 10% of all pregnant women around the world. This group of diseases and conditions includes pre-eclampsia and eclampsia, gestational hypertension and chronic hypertension (*4, 5*). Preeclampsia is responsible for complications in 2- 8% of pregnancies (*4, 5*). Outcomes of pre-eclampsia can result in death and morbidity, including poor growth, prematurity and asphyxia for the infant (*5*). Overall, pre-eclampsia and eclampsia are associated with 10- 15% of direct maternal deaths and most of deaths are caused by progression of pre-eclampsia to eclampsia (*5*). 9.1 % of all maternal deaths in Africa and Asia are associated with hypertensive disorders during pregnancy, while one out of four of maternal deaths in Latin America have been associated with this condition (*7*). Similarly, perinatal mortality is high both with pre-eclampsia and eclampsia (*7*).

2. Current public health interventions

Prevention of preterm delivery and gestational hypertensive disorders are a major focus of public health. Since these conditions have a multifactorial etiology, there are also several interventions aimed at their prevention.

The World Health Organization (WHO) recently published an evidence-informed guideline with 16 effective interventions to treat pre-eclampsia and eclampsia, in which calcium supplementation is included (*4*). An additional recent WHO guideline on calcium supplementation in pregnant women confirms this and also points out a possible protective effect of calcium on the prevention of preterm birth among those women who consumed between 1.5 g and 2.0 g of calcium per day (*8*). Daily iron and folic acid supplementation during pregnancy is other nutritional intervention that has shown to have a protective effect on low birth weight and very premature birth (*9*).

3. Proposed public health intervention

Given the most recent evidence available, a public health measure of daily calcium supplementation is recommended for pregnant women in order to reduce the risk of developing gestational hypertensive disorders and associated health problems.

III. Methods

1. Methods for the assessment of dosing, efficacy and safety

Two recent Cochrane systematic reviews investigated whether calcium supplements consumed on a daily basis during pregnancy safely improved maternal and infant outcomes. The meta-analyses included randomized published, unpublished and ongoing trials comparing different daily doses of calcium supplements with a placebo (*3, 10*)

2. Methods for the assessment of costs

Cost analysis was conducted for calcium supplements from MSH 2011 drug price indicator guide (*11*). The median supplier price was referenced; however, when the supplier price was not available, the median buyer price was used in the analysis.

3. Methods for the assessment of current availability amongst Member States

A survey of NEMLs of 20 LMICs was undertaken to determine availability of calcium supplements (*12*).

4. Assessment of the evidence

Two recent Cochrane systematic reviews of randomised clinical trials investigated whether calcium supplements consumed daily during pregnancy safely improved maternal and infant outcomes (*3*, *10*). The risk of bias of each study was evaluated following the Cochrane methodology while the overall quality of the evidence per outcome was assessed according to the GRADE methodology (*13*).

IV. Regulatory information on calcium supplements

Calcium supplements are not reviewed for safety or efficacy and are not approved for the sale as medications by the SRAs in US (FDA), Australia (TGA) and the UK (MHRA) (*14-16*). No additional specific analysis of regulatory status of calcium supplements was warranted. However, manufacturers of supplements must be registered entities and certified to adhere to good manufacturing practices (*17*).

There are several different salt formulations of calcium available in the market. Calcium carbonate has the highest content of elemental calcium (*17*) as presented in Table 1.

Table 1: Calcium salt formulations

Calcium salt	% elemental Calcium
Calcium Acetate	25
Calcium Carbonate	40
Calcium Citrate	21
Calcium Glubionate	6.5
Calcium Gluconate	9
Calcium Lactate	12

V. Analysis of costs

MSH 2011 Drug Price Indicator Guide median supplier prices were used to compile cost of calcium supplements (*11*). Two types of calcium salts for oral supplementation were found in the MSH guide (lactate and carbonate), shown in Table 2. The costs should be carefully interpreted as the MSH guide price may not be the final consumer price.

Table 2 - Cost analysis of calcium supplementation

Calcium salt	dosage	elemental calcium	cost per tablet (USD)*	cost/per day (1.5 grams elemental calcium)	number of tablets per day (to achieve 1.5 grams elemental calcium)	cost per month (USD)
Calcium Lactate	650mg	84.5mg	0.0199	0.353	18	10.60
Calcium	600mg	240mg	0.0213	0.13	6.5	4.00

Carbonate
*Median Buyer Prices

VI. Current NEML availability evaluation

NEMLs of 20 LMICs were reviewed to determine current availability of calcium supplements (*12*). Table 3 below shows that 12 of the 20 countries have at least one salt of calcium for oral administration on their respective NEMLs. Amongst the available salts, calcium carbonate is the most commonly available salt. The overall low availability and variation in the calcium salt is as expected since this formulation is not currently on the EML or EMLc, and most LMICs use the model WHO EML/EMLc to build their respective national formularies (*17*).

Table 3: Availability analysis of calcium supplements

#	Country	Calcium Supplement (tab/cap)
1	Angola	None
2	Bangladesh	None
3	Bhutan	Calcium Lactate 300mg
4	Central African Republic	None
5	China	Calcium Gluconate (unknown strength)
6	Democratic Republic of Congo	None
7	Ecuador	Yes (unknown salt and strength)
8	Fiji	Calcium Carbonate 500mg
9	Ghana	Calcium Carbonate 500mg
11	Honduras	Calcium Carbonate 1.25g
10	India	None
12	Kiribati	Calcium Lactate 300mg
13	Malaysia	None
14	Namibia	Calcium Gluconate 300mg
15	Oman	Calcium Carbonate 500mg, 600mg
16	Pakistan	None
17	Rwanda	None
18	Senegal	Calcium Carbonate 1g
19	Thailand	Calcium Carbonate (unknown strength)
20	Vanuatu	Yes (unknown salt and strength)

VII. Evidence on dosing, efficacy and safety of calcium supplementation

The results of two systematic reviews were combined to investigate whether calcium supplements consumed daily during pregnancy safely improve maternal and infant outcomes (*8*).

Twenty one randomized controlled trials (RCT), involving 19 736 pregnant women from both developed and developing countries in all continents, were included. These trials compared calcium supplementation with receiving a placebo or no intervention in addition to the regular antenatal care. The supplemental dose of calcium ranged between 300 mg (0.3 g) and 2000 mg (2 g) per day. Most of the studies started supplementation at the second trimester of pregnancy and were considered of high quality.

1. Quality of evidence

According to the GRADE methodology, the quality of the evidence for admission to neonatal intensive care unit was high, it was moderate for pre-eclampsia, eclampsia, high blood pressure, and maternal admission to intensive care unit, and it was low for maternal death, HELLP syndrome, preterm birth, low birth weight, and perinatal mortality (*8*).

2. Summary of the evidence

For all women, irrespective of the baseline risk of developing hypertension and calcium intake status, calcium supplementation more than halved the risk of pre-eclampsia when compared with a placebo (average risk ratio (RR) 0.48, 95% confidence interval (CI) 0.34-0.67, 15 trials, 16 490 women). This risk reduction was 41% for women at low-risk of developing hypertension (RR 0.59, 95% CI 0.42-0.82, 10 trials, 15 903 women) whereas the largest risk reduction (78%) was recorded among those at high risk of hypertensive disorders (RR 0.22, 95% CI 0.12-0.42, five trials, 587 women).

High blood pressure (with or without proteinuria) showed, in general, a similar pattern to that of pre-eclampsia. Overall, fewer women had high blood pressure when receiving calcium supplementation as compared to placebo (RR 0.65, 95% CI 0.53-0.81, 12 trials, 15 470 women). The reduction in risk of having high blood pressure was greatest among women at high risk of developing hypertension (RR 0.47, 95% CI 0.22-0.9, four trials, 327 women) and among those with a low baseline dietary calcium intake (RR 0.44, 95% CI 0.28-0.70, seven trials, 10 418 women).

There were no statistically significant differences between women supplemented with calcium and women receiving placebo or no treatment for eclampsia (RR 0.66, 95%

CI 0.40-1.11, five trials, 14 185 women). All these results remained similar when the analysis was restricted only to developing countries in a non-Cochrane review (*18*).

Among maternal adverse effects, there was a significant increase in the risk ratio for HELLP (haemolysis, elevated liver enzymes, low platelet counts) syndrome observed among women who received calcium supplementation compared to placebo (RR 2.67, 95% CI 1.05-6.82, two trials, 12 901 women). This is a rare condition that occurs in 10–20% of cases with severe pre-eclampsia (*19*). There were no effects on maternal death (RR 0.17, 95% CI 0.02-1.39, one trial, 8312 women) or maternal admission to the intensive care unit (RR 0.84, 95% CI 0.66-1.07, one trial, 8312 women).

In regard to infant outcomes, although overall there was no effect of calcium supplementation on preterm birth, a subgroup analysis by dose suggests that women who consumed 1.5 g of calcium per day or more had fewer preterm babies than those women who received 1.0 to 1.49 g of calcium or less than 1 g per day (RR 0.78 95% CI 0.63-0.98 vs. RR 0.14 95% CI 0.01-2.48 vs. RR 1.55 95% CI 1.00-2.48). There were no significant differences between women who received calcium supplements and those who did not in the risk of having low birth weight babies (RR 0.85, 95% CI 0.72-1.01, nine trials, 14 883 infants), being admitted to neonatal intensive care unit (RR 1.05, 95% CI 0.94 to 1.18, four trials, 13 406 women) and presenting stillbirth or neonatal death before hospital discharge (RR 0.90, 95% CI 0.74 to 1.09, 11 trials, 15 665 women).

Other than the occurrence of HELLP syndrome in 2 studies, the reviews did not yield information on side-effects with calcium supplementation (*3, 10*). However, calcium is generally well tolerated. Some mild side-effects such as headache, constipation, laxative effect, acid rebound, nausea, vomiting, anorexia, abdominal pain, xerostomia or flatulence may occur 1-10% of the time. Similarly, hypophosphatemia and hypercalcemia may also occur. High doses of calcium carbonate can lead to the milk-alkali syndrome, nephrocalcinosis and renal insufficiency. Calcium can interfere with the absorption of some other minerals such as iron or zinc, and with drugs such as bisphosphonates and tetracyclines. This interaction, however, can be easily managed by separating calcium supplementation from other medications/minerals by 2 hours or more (*20, 21).*

VIII. WHO guidelines on calcium supplementation

There are two recent WHO guidelines assessing the use of calcium supplements in pregnant women:

- WHO recommendations for the prevention and treatment of pre-eclampsia and eclampsia, published in 2011 (*4*), and
- Calcium supplementation in pregnant women, developed in 2012 (*8*).

In both guidelines, WHO makes a strong recommendation for supplementation fo pregnant women with 1.5 grams to 2.0 grams of elemental calcium per day in areas where dietary calcium intake is low and for women at high risk of developing hypertensive disorders during pregnancy (*4, 8*).

Suggested scheme for calcium supplementation in pregnant women (*8*)

Dosage	1.5–2.0 g elemental calcium/day[a]
Frequency	Daily
Duration	Supplementation may start at week 20 onwards
Target group	All pregnant women, particularly those at higher risk of hypertension[b]
Settings	Areas with low calcium intake

[a] 1 g of elemental calcium equals 2.5 g of calcium carbonate or 4 g of calcium citrate.

[b] Women are regarded as being at high risk of developing hypertension and pre-eclampsia if they have one or more of the following risk factors: obesity, previous pre-eclampsia, diabetes, chronic hypertension, renal disease, autoimmune disease, multiple pregnancy, and either adolescent or late pregnancy. This is not an exhaustive list, but can be adapted/complemented based on the local epidemiology of pre-eclampsia.

IX. Summary and recommendations

There is clear evidence to show that daily supplementation with 1.5 grams to 2 grams of elemental calcium is beneficial to reduce the risks of gestational hypertension, preeclampsia, and preterm birth.

Availability analysis shows that most nations tend to have some form of calcium on their NEMLs, although there is variability in the salt and dosage that may be addressed by

listing a specific formulation on the WHO model formulary. Furthermore, the cost analysis shows that calcium carbonate salt is the most economical supplement available at an approximated cost of USD 4.00 per month. Also since the carbonate salt contains the highest amount of elemental calcium content, the pill burden is lower with this formulation.

The recommendations for changes to the EML Section 27 – Vitamins and Minerals, are as follow:

2. Add 500 mg elemental calcium in the form of calcium carbonate to the EML.
a. Dose, frequency and duration: Take three (3) tablets three times a day preferably with meals, for the duration of the pregnancy to achieve daily intake of 1.5 grams of elemental calcium

X. References

1. World Health Organization, Food and Agricultural Organization of the United Nations. *Vitamin and mineral requirements in human nutrition*. Second edition. Geneva, World Health Organization, 2004 (http://www.who.int/nutrition/publications/micronutrients/9241546123/en/index.html , accessed 3 November 2010).
2. Villar J, Say L, Shennan A, Lindheimer M, Duley L, Conde-Agudelo A, et al. Methodological and technical issues related to the diagnosis, screening, prevention and treatment of pre-eclampsia and eclampsia. *International Journal of Gynecology & Obstetrics* 2004;85(Suppl 1):S28–S41.
3. Hofmeyr GJ, Lawrie TA, Atallah ÁN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. *Cochrane Database of Systematic Reviews 2010*, Issue 8. Art. No.: CD001059.
4. *WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia*. Geneva, Switzerland: World Health Organization, 2011.
5. Duley L. The global impact of pre-eclampsia and eclampsia. Seminars in perinatology. 2009;33(3):130-7. Epub 2009/05/26.
6. *Trends in maternal mortality: 1990 to 2008: estimates developed by WHO, UNICEF, UNFPA and the World Bank*. Geneva, World Health Organization, 2010 (http://www.who.int/reproductivehealth/publications/monitoring/9789241500265/en, accessed 3 November 2010).
7. Khan KS et al. WHO analysis of causes of maternal death: a systematic review. Lancet, 2006, 367:1066–1074.)
8. *Guideline: Calcium supplementation in pregnant women*. Geneva, World Health Organization, 2012 (in press).
9. Peña-Rosas JP, De-Regil LM, Dowswell T, Viteri FE. Daily oral iron supplementation during pregnancy. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD004736. DOI: 10.1002/14651858.CD004736.pub4.
10. Buppasiri P, Lumbiganon P, Thinkhamrop J, Ngamjarus C, Laopaiboon M. Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes. *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No.: CD007079.
11. MSH. International Drug Price Indicator Guide. Management Sciences for Health, 2011.
12. *National Medicines List/Formulary/Standard Treatment Guidelines*. World Health Organization; 2012 [cited 2012 November 1st]; Available from: http://www.who.int/selection_medicines/country_lists/en/index.html.
13. GRADE. GRADE Working Group. 2012 [cited 2012 November 5th]; Available from: http://www.gradeworkinggroup.org/.
14. FDA. Food and Drug Administration (FDA). 2012 [cited 2012 November 1st]; Available from: www.fda.gov.
15. TGA. Therapeutic Goods Administration (TGA). 2012 [cited 2012 November 1st]; Available from: www.tga.gov.au.

16. MHRA. United Kingdom - Medicines and Healthcare Products Regulatory Agency. 2012 [cited 2012 November 1st]; Available from: http://www.mhra.gov.uk/.
17. Micromedex 2.0 - Clinical Pharmacy Database [database on the Internet]. 2012 [cited October 1st, 2012]. Available from: www.micromedex.com.
18. Imdad A, Bhutta ZA. Effects of calcium supplementation during pregnancy on maternal, fetal and birth outcomes. Paediatric and Perinatal Epidemioly. 2012 Jul;26 Suppl 1:138-52
19. Haram K, Svendsen E, Abildgaard U. The HELLP syndrome: clinical issues and management. A Review. BMC Pregnancy Childbirth 2009,26;9:8 (http://www.biomedcentral.com/1471-2393/9/8/, accessed 25 June 2012)
20. Laing R, Waning B, Gray A, Ford N, t Hoen E. 25 years of the WHO essential medicines lists: progress and challenges. Lancet. 2003;361(9370):1723-9. Epub 2003/05/28.
21. Lexi-Comp Online Database [database on the Internet]. 2012 [cited October 1st, 2012]. Available from: www.lexi.com.

Appendix A: Summary of Findings (GRADE) tables

Table 1. Routine calcium supplementation for pregnant women: maternal outcomes

Patient or population: Pregnant women

Settings: all settings

Intervention: calcium supplementation

Comparison: placebo or no intervention

Outcomes	Relative effect or mean difference (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Pre-eclampsia	RR 0.48 (0.34–0.67)	16 490 (15 trials)	⊕⊕⊕⊖ **moderate**[1]	
Eclampsia	RR 0.66 (0.40-1.11)	14 185 (5 trials)	⊕⊕⊕⊖ **moderate**[1,2]	
High blood pressure (with or without proteinuria)*	RR 0.65 (0.53-0.81)	15 470 (12 trials)	⊕⊕⊕⊖ **moderate**[1]	
Maternal death*♣	RR 0.17 (0.02–1.39)	8312 (1 trial)	⊕⊕⊖⊖ **low**[2,,3]	
Maternal admission to intensive care unit*♣	0.84 (0.66-1.07)	8312 (1 trial)	⊕⊕⊕⊖ **moderate**[3]	
HELLP syndrome*	RR 2.67 (1.05–6.82)	12901 (2 trials)	⊕⊕⊕⊖ **low**[2,4]	

CI, confidence interval; RR, risk ratio; MD, mean difference.

*GRADE Working Group grades of evidence:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We have moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

[1] Serious statistical heterogeneity possibly due to variation in baseline dietary intake of calcium, but there is consistency in the direction of the effect.

[2] Wide confidence intervals (imprecision).

[3] Only one study reported on this outcome.

[4] Few events.

* For details of studies included in the review, see reference (*3*).

♣ For details of studies included in the review, see reference (*9*).

Table 2. Routine calcium supplementation for pregnant women: newborn outcomes

Patient or population: Pregnant women

Settings: all settings

Intervention: calcium supplementation

Comparison: placebo or no intervention

Outcomes	Relative effect or mean difference (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Preterm birth	RR 0.83 (0.66, 1.04)	16 093 (14 trials)	⊕⊕⊕⊖ **low**[1,2]	
Low birth weight*	RR 0.85 (0.72–1.01)	14 883 (9 trials)	⊕⊖⊖⊖ **low**[1,2]	
Perinatal mortality♣	RR 0.84 (0.61–1.16)	5 145 (7 trials)	⊕⊖⊖⊖ **low**[1,2]	
Admission to neonatal intensive care unit*♣	RR 1.05 (0.94–1.18)	14 062 (4 trials)	⊕⊕⊕⊕ **high**	

CI, confidence interval; RR, risk ratio; MD, mean difference.

*GRADE Working Group grades of evidence:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We have moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

[1] Serious statistical heterogeneity (61%) possibly explained by the supplemental dose of calcium, but there is consistency in the direction of the effect.

[2] There are some trials at high risk of bias, particularly due to high loses to follow up and lack of blinding.

* For details of studies included in the review, see reference (*3*).

♣ For details of studies included in the review, see reference (*9*).