ClinicalEvidence

Pre-eclampsia: reducing the risk with calcium supplements

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ABSTRACT

INTRODUCTION: Pre-eclampsia (raised blood pressure and proteinuria) complicates 2% to 8% of pregnancies, and increases morbidity and mortality in the mother and child. Pre-eclampsia is more common in older women, women with a high body mass index, and women with multiple pregnancy. Pre-eclampsia risk is also increased in women with underlying medical conditions, particularly conditions associated with microvascular disease. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical questions: Does oral calcium supplementation during pregnancy reduce the risk and/or severity of pre-eclampsia? What are the effects of preventive calcium supplements pre-conception in women at risk of pre-eclampsia? We searched: Medline, Embase, The Cochrane Library, and other important databases up to November 2014 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). RESULTS: At this update, searching of electronic databases retrieved 109 studies. After deduplication and removal of conference abstracts, 55 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 30 studies and the further review of 25 full publications. Of the 25 full articles evaluated, one update of a previously included systematic review was added. We performed a GRADE evaluation for seven PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for three interventions based on information about the effectiveness and safety of calcium supplementation used to prevent pre-eclampsia, both during pregnancy and pre-conception, and different doses of calcium supplementation versus each other during pregnancy.

QUESTIONS

INTERVENTIONS

ORAL CALCIUM SUPPLEMENTATION DURING PREGNANCY

Beneficial

Unknown effectiveness

PREVENTIVE CALCIUM SUPPLEMENTS PRE-CONCEPTION IN WOMEN AT RISK OF PRE-ECLAMPSIA

Unknown effectiveness

Key points

- Pre-eclampsia (raised blood pressure and proteinuria) complicates 2% to 8% of pregnancies, and increases morbidity and mortality in the mother and child.

  Pre-eclampsia is more common in older women, women with a high body mass index, and women with multiple pregnancy. Pre-eclampsia risk is also increased in women with underlying medical conditions, particularly conditions associated with microvascular disease (e.g., chronic hypertension, diabetes, renal disease, and autoimmune conditions).

- Despite countless studies, few therapies have been found to reduce the risk of developing pre-eclampsia. The use of low-dose aspirin has been shown to be one such therapy. For this update, we have focused on evidence from RCTs and systematic reviews of RCTs on the effect of calcium supplementation on the risk and/or severity of pre-eclampsia.

- The use of calcium supplementation during pregnancy reduces the risk of pre-eclampsia and pre-term birth compared with placebo. It also seems to reduce maternal mortality/serious morbidity.

  However, there was no difference in the incidence of eclampsia, placental abruption, caesarean section, stillbirth or neonatal death, or low birth weight (birth weight <2500 g), or need for further maternal or neonatal interventions or intensive care, in the calcium supplementation group.

  The beneficial effect of calcium supplementation is particularly marked in those women with a low-calcium diet.

- We found no systematic review or RCT evidence for different doses of calcium supplements versus each other or for pre-conceptual calcium supplementation.

Clinical context

GENERAL BACKGROUND

Pre-eclampsia (raised blood pressure and proteinuria) complicates 2% to 8% of pregnancies, and increases morbidity and mortality in the mother and child. It is more common in older women, women with a high body mass index, and women with multiple pregnancy. Pre-eclampsia risk is also increased in women with underlying medical conditions, particularly conditions associated with microvascular disease (e.g., chronic hypertension, diabetes, renal disease, and autoimmune conditions).

FOCUS OF THE REVIEW

Despite countless studies, few therapies have been found to reduce the risk of developing pre-eclampsia. The use of low-dose aspirin has been shown to be one such therapy and is now advocated by the National Institute for Health and Care Excellence (NICE) in women considered at high risk of developing pre-eclampsia. Less evidence is available for calcium supplementation and, therefore, this therapy has been chosen as a focus for this overview.

COMMENTS ON EVIDENCE

This overview indicates that the use of calcium supplementation does reduce the risk of pre-eclampsia, pre-term birth, and the composite outcome of maternal death or severe morbidity. Although most trials in the systematic review were of good quality, they included only nulliparous or primiparous women and were conducted largely in the US and South America, with most women classified at low risk of pre-eclampsia and with low dietary calcium. While not necessarily applicable to the UK population, this evidence supports the use of calcium supplementation in women with low-calcium diets and those at higher risk of pre-eclampsia. The timing of starting these supplements and the adherence to the high doses used, which are often unpalatable and unacceptable to women, needs further research.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, February 2010, to November 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 109 studies. After deduplication and removal of conference abstracts, 55 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 30 studies and the further review of 25 full publications. Of the 25 full articles evaluated, one update of a previously included systematic review was added.

ADDITIONAL INFORMATION

The evidence has led to the World Health Organisation recommending calcium supplementation of 1.5 to 2.0 g daily for pregnant women with low-calcium diets.

DEFINITION

Hypertension in pregnancy is defined as blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic occurring twice and at least 4 hours apart. Hypertension during pregnancy may be classified [1] as: **Chronic hypertension** known hypertension before pregnancy or raised blood pressure before 20 weeks' gestation. It may be essential hypertension or, less commonly, secondary to an underlying disease. [2] **Gestational hypertension** new-onset raised blood pressure, without evidence of other complications of pre-eclampsia. **Pre-eclampsia** new or worsening hypertension usually after 20 weeks' gestation, in association with new or worsening proteinuria; other maternal organ dysfunction (notably renal, liver, haematological, or neurological); and/or evidence of fetal growth restriction. This may be de novo or superimposed on chronic hypertension. **White coat hypertension** diagnosed by evidence of hypertension during clinic visits but demonstration of normal blood pressure, ideally using 24-hour ambulatory BP monitoring (ABPM), in the first half of pregnancy.

INCIDENCE/ PREVALENCE

Pregnancy-induced hypertension affects 10% of pregnancies, and pre-eclampsia complicates 2% to 8% of pregnancies. [3] Eclampsia occurs in about 1/2000 deliveries in resource-rich countries. [4] In resource-poor countries, estimates of the incidence of eclampsia vary from 1/100 to 1/1700. [5] [6]

AETIOLOGY/ RISK FACTORS

The aetiology of pre-eclampsia is only partially understood. It is likely to be multifactorial, and may result from deficient placental implantation during the first half of pregnancy. [7] Pre-eclampsia is more common among women with multiple pregnancy, obesity, or older age and among women with medical conditions associated with microvascular disease (such as diabetes, hypertension, and autoimmune conditions). [8] [9] One systematic review found that the risk of pre-eclampsia is increased in women with a previous history of pre-eclampsia (RR 7.19, 95% CI 5.85 to 8.83) and in those with antiphospholipid antibodies (RR 9.72, 95% CI 4.34 to 21.75), pre-existing diabetes (RR 3.56, 95% CI 2.54 to 4.99), multiple (twin) pregnancy (RR 2.93, 95% CI 2.04 to 4.21), nulliparity (RR 2.91, 95% CI 1.28 to 6.61), family history (RR 2.90, 95% CI 1.70 to 4.93), raised blood pressure (diastolic 80 mm Hg or greater) at booking (RR 1.38, 95% CI 1.01 to 1.87), raised body mass index before pregnancy (RR 2.47, 95% CI 1.66 to 3.67) or at booking (RR 1.55, 95% CI 1.28

to 1.88), or maternal age 40 years or older (RR 1.96, 95% CI 1.34 to 2.87, for multiparous women). The review reported that other factors that increase the risk are: an interval of 10 years or more since a previous pregnancy; autoimmune disease; renal disease; and chronic hypertension. [10] Cigarette smoking seems to be associated with a lower risk of pre-eclampsia, but this potential benefit is outweighed by an increase in adverse outcomes such as low birth weight, placental abruption, and perinatal death. [11] **Predictive tests** Risk assessment using the risk factors discussed above is advocated by NICE at the booking visit to help risk-stratify women. Other investigations during pregnancy are used widely in clinical practice. A systematic review of the accuracy of 27 predictive tests for pre-eclampsia found that some seemed to have high specificity, but at the expense of compromised sensitivity. [12] The review reported that tests with specificity of more than 90% were: body mass index greater than 34, alpha-fetoprotein, and uterine artery Doppler (bilateral notching). The review found that the only Doppler test with a sensitivity of more than 60% was resistance index and combinations of indices. It also found that a few tests not commonly seen in routine practice (kallikreinuria and SDS-PAGE proteinuria) potentially have both high sensitivity and specificity, but these require further investigation. [12] Most recently, commercially available assays for plasma placentally derived growth factor (PlGF) have become available. In women with suspected pre-term pre-eclampsia, low (<fifth centile) plasma PlGF has high sensitivity and negative predictive value for pre-eclampsia within 14 days and is better than other currently used tests. [13]

PROGNOSIS

The outcome of pregnancy in women with late-onset pregnancy-induced hypertension alone is similar to that for normotensive pregnancies. [8] [14] However, once pre-eclampsia develops, morbidity and mortality increase for both mother and child. For example, perinatal mortality for women with severe pre-eclampsia is double that for normotensive women. [8] Perinatal outcome is worse with early gestational hypertension. [8] [14] [15] Perinatal mortality also increases in women with severe essential hypertension. [16]

AIMS OF INTERVENTION

To delay or prevent the development of pre-eclampsia and/or reduce the severity of pre-eclampsia, to improve outcomes for women and their babies.

OUTCOMES

For the woman: **mortality**; **morbidity** (such as renal failure, coagulopathy, cardiac failure, liver failure, placental abruption, and stroke); **development of pre-eclampsia** (rates of severe hypertension, rates of pre-eclampsia, proteinuria, and hypertension); **seizures** (includes eclampsia); **need for further interventions** (caesarean section); **use of resources** (such as dialysis, ventilation, admission to intensive care, or length of stay); **adverse effects**. For the child: **mortality**, intrauterine growth restriction, **preterm birth**, and **morbidity** (such as intraventricular haemorrhage, respiratory distress syndrome, or asphyxia, small for gestational age); measures of infant and **child development** (such as cerebral palsy or significant learning disability); **use of resources** (such as admission to a special care nursery, ventilation, length of stay in hospital, and special needs in the community); **adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date November 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to November 2014, Embase 1980 to November 2014, The Cochrane Database of Systematic Reviews 2014, issue 11 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, at least single-blinded, of any number of individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the review. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' sections (see below). **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment

section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported questions: What are the effects of preventive interventions in women at risk of pre-eclampsia? What are the effects of interventions in women who develop mild to moderate hypertension during pregnancy? What are the effects of interventions in women who develop severe pre-eclampsia or very high blood pressure during pregnancy? What is the best choice of anticonvulsant for women with eclampsia? We have added the following questions: Does oral calcium supplementation during pregnancy reduce the risk and/or severity of pre-eclampsia? What are the effects of preventive calcium supplements pre-conception in women at risk of pre-eclampsia? **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 12). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **Does oral calcium supplementation during pregnancy reduce the risk and/or severity of pre-eclampsia?**

OPTION **CALCIUM SUPPLEMENTATION VERSUS PLACEBO IN PREGNANT WOMEN AT RISK OF PRE-ECLAMPSIA**

- For GRADE evaluation of interventions for Pre-eclampsia: reducing the risk with calcium supplements, see table, p 12 .
- The use of calcium supplementation during pregnancy reduces the risk of pre-eclampsia and pre-term birth compared with placebo. It also seems to reduce maternal mortality/serious morbidity.
- However, there was no difference in the incidence of eclampsia, placental abruption, caesarean section, stillbirth or neonatal death, or low birth weight (birth weight <2500 g), or need for further maternal or neonatal interventions or intensive care, in the calcium supplementation group.
- The beneficial effect of calcium supplementation is particularly marked in those women with a low-calcium diet.
- The review reported an increase in the risk of HELLP (haemolysis, elevated liver enzymes, and low platelets) in the calcium group. However, it is difficult to draw any conclusions from this, due to the event rate being so low.

Benefits and harms

Calcium supplementation versus placebo:

We found one systematic review (search date 2013, 13 RCTs, 15,730 women). [17] Most trials in the systematic review were of good quality and included nulliparous or primiparous women. They were conducted largely in the US and South America. They included mainly women at low risk of pre-eclampsia, with low dietary calcium (see Comment, p 4 , below).

Mortality

Calcium supplementation compared with placebo Calcium supplements seem more effective at reducing the risk of maternal death or serious morbidity compared with placebo; however, they seem no more effective at reducing stillbirth or death of the baby before discharge from hospital (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maternal death or serious morbidity					
[17] Systematic review	Women with low dietary calcium 4 RCTs in this analysis	**Maternal mortality/serious morbidity** 167/4856 (3%) with calcium supplementation 210/4876 (4%) with placebo	RR 0.80 95% CI 0.65 to 0.97	●○○	calcium supplementation
Stillbirth or neonatal death before discharge					
[17] Systematic review	Babies 11 RCTs in this analysis	**Stillbirth or death of the baby before hospital discharge** 183/7821 (2%) with calcium supplementation 205/7844 (3%) with placebo	RR 0.90 95% CI 0.74 to 1.09	⟷	Not significant
[17] Systematic review	Babies born to women with low dietary calcium 7 RCTs in this analysis Subgroup analysis	**Stillbirth or death of the baby before hospital discharge** 154/5312 (3%) with calcium supplementation 179/5320 (3%) with placebo	RR 0.86 95% CI 0.70 to 1.07	⟷	Not significant
[17] Systematic review	Babies born to mothers with normal dietary calcium 4 RCTs in this analysis Subgroup analysis	**Stillbirth or death of the baby before hospital discharge** 29/2509 (1%) with calcium supplementation 26/2524 (1%) with placebo	RR 1.12 95% CI 0.66 to 1.90	⟷	Not significant

Preterm birth

Calcium supplementation compared with placebo Calcium supplementation is more effective at reducing preterm birth compared with placebo (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Preterm birth					
[17] Systematic review	Women 11 RCTs in this analysis	**Preterm birth** 722/7620 (9%) with calcium supplementation 795/7655 (10%) with placebo	RR 0.76 95% CI 0.60 to 0.97	●○○	calcium supplementation
[17] Systematic review	Women with low dietary calcium 7 RCTs in this analysis Subgroup analysis	**Preterm birth** 457/5111 (9%) with calcium supplementation 523/5131 (10%) with placebo	RR 0.81 95% CI 0.64 to 1.02	⟷	Not significant
[17] Systematic review	Women with normal dietary calcium 4 RCTs in this analysis Subgroup analysis	**Preterm birth** 265/2509 (11%) with calcium supplementation 272/2524 (11%) with placebo	RR 0.59 95% CI 0.26 to 1.33	⟷	Not significant

Morbidity

Calcium supplementation compared with placebo Calcium supplementation is no more effective at reducing the proportion of women with placental abruption or the number of babies born with a birth weight of below 2500 g compared with placebo (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maternal morbidity					
[17] Systematic review	Women 5 RCTs in this analysis	**Placental abruption** 36/7158 (1%) with calcium supplementation 42/7178 (1%) with placebo	RR 0.86 95% CI 0.55 to 1.34	⟷	Not significant
[17] Systematic review	Women with low dietary calcium 2 RCTs in this analysis Subgroup analysis	**Placental abruption** 23/4744 (1%) with calcium supplementation 26/4762 (1%) with placebo	RR 0.89 95% CI 0.51 to 1.55	⟷	Not significant
[17] Systematic review	Women with normal dietary calcium 3 RCTs in this analysis Subgroup analysis	**Placental abruption** 13/2414 (1%) with calcium supplementation 16/2416 (1%) with placebo	RR 0.81 95% CI 0.39 to 1.68	⟷	Not significant
Infant morbidity					
[17] Systematic review	Women 9 RCTs in this analysis	**Birth weight <2500 g** 810/7433 (11%) with calcium supplementation 878/7450 (12%) with placebo	RR 0.85 95% CI 0.72 to 1.01	⟷	Not significant
[17] Systematic review	Women with low dietary calcium 5 RCTs in this analysis Subgroup analysis	**Birth weight <2500 g** 607/4924 (12%) with calcium supplementation 636/4926 (13%) with placebo	RR 0.95 95% CI 0.85 to 1.05	⟷	Not significant
[17] Systematic review	Women with normal dietary calcium 4 RCTs in this analysis Subgroup analysis	**Birth weight <2500 g** 203/2509 (8%) with calcium supplementation 242/2524 (10%) with placebo	RR 0.59 95% CI 0.31 to 1.13	⟷	Not significant

Child development

No data from the following reference on this outcome. [17]

Development of pre-eclampsia

Calcium supplementation compared with placebo Calcium supplementation is more effective at reducing the risk of pre-eclampsia compared with placebo, especially in women with low dietary calcium or who are at a high risk of developing pre-eclampsia (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Development of pre-eclampsia					
[17] Systematic review	Women 13 RCTs in this analysis	**Pre-eclampsia** 379/7851 (5%) with calcium supplementation 510/7879 (6%) with placebo	RR 0.45 95% CI 0.31 to 0.65	●●○	calcium supplementation

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[17] Systematic review	Women with low dietary calcium 8 RCTs in this analysis Subgroup analysis	**Pre-eclampsia** 209/5331 (4%) with calcium supplementation 306/5347 (6%) with placebo	RR 0.36 95% CI 0.20 to 0.65	●●○	calcium supplementation
[17] Systematic review	Women with normal dietary calcium 4 RCTs in this analysis Subgroup analysis	**Pre-eclampsia** 169/2505 (7%) with calcium supplementation 197/2517 (8%) with placebo	RR 0.62 95% CI 0.32 to 1.20	⟷	Not significant
[17] Systematic review	Women at high risk of pre-eclampsia 5 RCTs in this analysis Subgroup analysis	**Pre-eclampsia** 9/281 (3%) with calcium supplementation 54/306 (18%) with placebo	RR 0.22 95% CI 0.12 to 0.42	●●○	calcium supplementation
[17] Systematic review	Women at normal risk of pre-eclampsia 8 RCTs in this analysis Subgroup analysis	**Pre-eclampsia** 370/7570 (5%) with calcium supplementation 456/7573 (6%) with placebo	RR 0.59 95% CI 0.41 to 0.83	●○○	calcium supplementation

Seizures

Calcium supplementation compared with placebo Calcium supplementation is no more effective at reducing the risk of eclampsia compared with placebo (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Eclampsia					
[17] Systematic review	Women 3 RCTs in this analysis	**Eclampsia** 21/6719 (0.3%) with calcium supplementation 29/6706 (0.4%) with placebo	RR 0.73 95% CI 0.41 to 1.27	⟷	Not significant
[17] Systematic review	Women with low dietary calcium 2 RCTs in this analysis Subgroup analysis	**Eclampsia** 17/4424 (<1%) with calcium supplementation 25/4412 (<1%) with placebo	RR 0.68 95% CI 0.37 to 1.26	⟷	Not significant
[17] Systematic review	4589 women with normal dietary calcium Data from 1 RCT Subgroup analysis	**Eclampsia** 4/2295 (<1%) with calcium supplementation 4/2294 (<1%) with placebo	RR 1.00 95% CI 0.25 to 3.99	⟷	Not significant

Need for further interventions

Calcium supplementation compared with placebo Calcium supplements are no more effective at reducing the risk of caesarean delivery compared with placebo (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Caesarean delivery					
[17] Systematic review	Women 8 RCTs in this analysis	**Caesarean delivery** 1345/7608 (18%) with calcium supplementation 1413/7626 (19%) with placebo	RR 0.95 95% CI 0.89 to 1.02	⟷	Not significant
[17] Systematic review	Women with low dietary calcium 5 RCTs in this analysis Subgroup analysis	**Caesarean delivery** 917/5124 (18%) with calcium supplementation 960/5129 (19%) with placebo	RR 0.96 95% CI 0.88 to 1.04	⟷	Not significant
[17] Systematic review	Women with normal dietary calcium 3 RCTs in this analysis Subgroup analysis	**Caesarean delivery** 428/2484 (17%) with calcium supplementation 453/2497 (18%) with placebo	RR 0.95 95% CI 0.84 to 1.07	⟷	Not significant

Use of resources

Calcium supplementation compared with placebo Calcium supplementation is no more effective than placebo at reducing admission of neonates or mothers to intensive or high-care facilities (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Maternal use of resources: admission to intensive care facility					
[17] Systematic review	8312 women with low dietary calcium Data from 1 RCT	**Admission of mothers to an intensive care unit** 116/4151 (3%) with calcium supplementation 138/4161 (3%) with placebo	RR 0.84 95% CI 0.66 to 1.07	⟷	Not significant
Neonatal use of resources: admission to neonatal high care facility					
[17] Systematic review	Women 4 RCTs in this analysis	**Admission of neonates to a high-care facility** 530/6689 (8%) with calcium supplementation 507/6717 (8%) with placebo	RR 1.05 95% CI 0.94 to 1.18	⟷	Not significant
[17] Systematic review	Women with low dietary calcium 3 RCTs in this analysis Subgroup analysis	**Admission of neonates to a high-care facility** 187/4526 (4%) with calcium supplementation 192/4544 (4%) with placebo	RR 0.98 95% CI 0.81 to 1.19	⟷	Not significant
[17] Systematic review	4336 women with normal dietary calcium Data from 1 RCT Subgroup analysis	**Admission of neonates to a high-care facility** 343/2163 (16%) with calcium supplementation 315/2173 (14%) with placebo	RR 1.09 95% CI 0.95 to 1.26	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [17]

Further information on studies

[17] There was an anomalous increase in the risk of HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome (2 trials, 12,901 women: RR 2.67, 95% CI 1.05 to 6.82; $I^2 = 0\%$) in the calcium group; however, the absolute number of events was low (16 with calcium *v* 6 without). Several studies reported that adherence to treatment was 60% to 90%. The proportion of women taking 90% to 100% of all allocated treatment was 85% in the largest study, but low in several others (20% in 1 study). The statistical heterogeneity for some outcomes seemed to be explained by differences between the small and large trials, with small trials of largely high-risk women having more positive results. The review identified no RCTs comparing high-dose versus low-dose calcium supplementation. However, four RCTs were identified that assessed the effects of supplementation with a low dose of calcium (<1 g) compared with placebo. The baseline level of dietary calcium across the studies was unclear. The authors of the review noted that supplementation with low doses of calcium reduced the risk of pre-eclampsia, hypertension, low birthweight, and neonatal intensive care unit admission. However, most studies recruited women at high risk for pre-eclampsia, and were at high risk of bias, and the authors commented that results should be interpreted with caution.

Comment:

Clinical guide

This review indicates that the use of calcium supplementation does reduce the risk of pre-eclampsia, pre-term birth, and the composite outcome of maternal death or severe morbidity. Although most trials in the systematic review were of good quality, they included only nulliparous or primiparous women and were conducted largely in the US and South America, with most women classified at low risk of pre-eclampsia and with low dietary calcium. Therefore, questioning applicability to the UK population should be acknowledged. Rightly, the authors also state that the treatment effect may be overestimated due to small-study effects or publication bias.

That said, the reduction in pre-term birth, particularly in the women considered at high risk of pre-eclampsia, is suggestive that calcium supplementation may delay/reduce the severity of pre-eclampsia such that iatrogenic pre-term birth is reduced. This has huge clinical (physical and psychological) and economic importance to both mother and baby in the short and longer term.

In clinical practice there is no time to accurately assess a woman's calcium intake with currently validated questionnaires for this purpose. So, while it is interesting that the effect size was particularly in women with low-calcium diet, in practice this information is currently of little clinical utility, and research to simplify identification of such women would be valuable.

The timing of starting these supplements, and the adherence to the high doses used, which are often unpalatable and unacceptable to women, needs further research.

Of note, this review reported an increase in the risk of HELLP (haemolysis, elevated liver enzymes, and low platelets) in the calcium group that reached statistical significance. However, it is difficult to draw any conclusions from this, as the event rate was so small (16/6466 [0.002%] in the calcium group versus 6/6455 [0.001%] in the control group). It is well known that dietary calcium enrichment lowers blood pressure in animal and human studies. One plausible explanation could be that women in the calcium group had lower blood pressure and, therefore, were delivered later, allowing an increased likelihood of progression to HELLP. However, as the authors conclude, the magnitude of the benefit of calcium, including a reduction in maternal mortality and serious morbidity, is considered to outweigh the increased risk of HELLP syndrome given the small event rate.

The evidence has led to the WHO recommending calcium supplementation of 1.5 to 2.0 g daily for pregnant women with low-calcium diets, and this evidence should be considered when NICE update their hypertension in pregnancy guidelines.

OPTION DIFFERENT DOSES OF CALCIUM SUPPLEMENTATION VERSUS EACH OTHER IN PREGNANT WOMEN AT RISK OF PRE-ECLAMPSIA New

- For GRADE evaluation of interventions for Pre-eclampsia: reducing the risk with calcium supplements, see table, p 12 .

- We found no direct information from RCTs on how different doses of calcium supplements compare with each other in terms of their effectiveness at reducing pre-eclampsia and related outcomes.

Benefits and harms

Different doses of calcium supplementation versus each other:

We found no systematic review or RCTs.

Comment: None.

QUESTION **What are the effects of preventive calcium supplements pre-conception in women at risk of pre-eclampsia?**

OPTION **PRE-CONCEPTION CALCIUM SUPPLEMENTATION VERSUS PLACEBO IN WOMEN AT RISK OF PRE-ECLAMPSIA** New

- For GRADE evaluation of interventions for Pre-eclampsia: reducing the risk with calcium supplements, see table, p 12 .
- We found no direct information from RCTs on how pre-conception calcium supplements compare with placebo in terms of their effectiveness at reducing pre-eclampsia and related outcomes.

Benefits and harms

Calcium supplementation versus placebo:

We found no systematic review or RCTs evaluating the effects of taking calcium supplements pre-conception on developing pre-eclampsia.

Comment: **Clinical guide**

The prescribing and taking of medications in anticipation of a pregnancy is complicated by the high rates of unplanned pregnancies in many countries. Adherence to folic acid in the pre-conceptual period is still patchy, and until there are better strategies and education to facilitate this health behaviour, even evidence-based therapies are unlikely to have good adherence.

However, with an increasing appreciation, both in research and clinical practice, of the importance of the pre-conceptual period, this research question is an important consideration.

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

SUBSTANTIVE CHANGES

Different doses of calcium supplementation versus each other in pregnant women at risk of pre-eclampsia New option. No evidence found. Categorised as 'unknown effectiveness'.

Pre-conception calcium supplementation versus placebo in women at risk of pre-eclampsia New option. No evidence found. Categorised as 'unknown effectiveness'.

Calcium supplementation versus placebo in pregnant women at risk of pre-eclampsia One systematic review updated. [17] Evidence re-evaluated. Categorisation unchanged (beneficial).

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Disclaimer

GRADE **Evaluation of interventions for Pre-eclampsia: reducing the risk with calcium supplements.**

Important outcomes	**Child development, Development of pre-eclampsia, Morbidity, Mortality, Need for further interventions, Preterm birth, Seizures, Use of resources**								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
Does oral calcium supplementation during pregnancy reduce the risk and/or severity of pre-eclampsia?									
11 at most (15,665 at most) [17]	Mortality	Calcium supplementation versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for use of a composite outcome for maternal mortality
11 (15,275) [17]	Preterm birth	Calcium supplementation versus placebo	4	0	0	0	0	High	
9 (14,883) [17]	Morbidity	Calcium supplementation versus placebo	4	0	0	0	0	High	
13 (15,730) [17]	Development of pre-eclampsia	Calcium supplementation versus placebo	4	0	0	0	+1	High	Effect-size point added for RR <0.5
3 (13,425) [17]	Seizures	Calcium supplementation versus placebo	4	0	0	0	0	High	
8 (15,234) [17]	Need for further interventions	Calcium supplementation versus placebo	4	0	0	0	0	High	
4 (13,406) [17]	Use of resources	Calcium supplementation versus placebo	4	0	0	0	0	High	

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.