Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for leg cramps in pregnancy (Review)

Zhou K, West HM, Zhang J, Xu L, Li W

Zhou K, West HM, Zhang J, Xu L, Li W.
Interventions for leg cramps in pregnancy.
Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CD010655.
DOI: 10.1002/14651858.CD010655.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Interventions for leg cramps in pregnancy

Kunyan Zhou[1], Helen M West[2], Jing Zhang[1], Liangzhi Xu[1], Wenjuan Li[1]

[1]Department of Obstetrics and Gynecology, West China Second University Hospital, West China Women's and Children's Hospital, Chengdu, China. [2]Cochrane Pregnancy and Childbirth Group, Department of Women's and Children's Health, The University of Liverpool, Liverpool, UK

Contact address: Liangzhi Xu, Department of Obstetrics and Gynecology, West China Second University Hospital, West China Women's and Children's Hospital, No. 20, 3rd section, People South Road, Chengdu, Sichuan, China. liangzxu@126.com.

Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New, published in Issue 8, 2015.

Citation: Zhou K, West HM, Zhang J, Xu L, Li W. Interventions for leg cramps in pregnancy. *Cochrane Database of Systematic Reviews* 2015, Issue 8. Art. No.: CD010655. DOI: 10.1002/14651858.CD010655.pub2.

ABSTRACT

Background

Leg cramps are a common problem in pregnancy. Various interventions have been used to treat them, including drug, electrolyte and vitamin therapies, and non-drug therapies.

Objectives

To assess the effectiveness and safety of different interventions for treating leg cramps in pregnancy.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Register (31 March 2015) and reference lists of retrieved studies.

Selection criteria

Randomised controlled trials (RCTs) of any intervention (drug, electrolyte, vitamin or non-drug therapies) for treatment of leg cramps in pregnancy compared with placebo, no treatment or other treatment. Quinine was excluded for its known adverse effects (teratogenicity). Cluster-RCTS were considered for inclusion. Quasi-RCTs and cross-over studies were excluded.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy.

Main results

We included six studies (390 women). Four trials compared oral magnesium with placebo/no treatment, two compared oral calcium with no treatment, one compared oral vitamin B versus no treatment, and one compared oral calcium with oral vitamin C. Two of the trials were well-conducted and reported, the other four had design limitations. The process of random allocation was sub-optimal in three studies, and blinding was not attempted in two. Outcomes were reported in different ways, precluding the use of meta-analysis and limiting the strength of our conclusions.

The 'no treatment' group in one four-arm trial has been used as the comparison group for the composite outcome (intensity and frequency of leg cramps) in magnesium, calcium, and vitamin B versus no treatment. This gives it disproportionate weight in the overall analysis, thus interpretation of these results should be cautious.

Oral magnesium versus placebo/no treatment

Magnesium (taken orally for two to four weeks) did not consistently reduce the frequency of leg cramps compared with placebo or no treatment. Outcomes that showed differences were: **frequency of leg cramps** after treatment: never, and twice a week (risk ratio (RR) 5.66, 95% confidence interval (CI) 1.35 to 23.68, one trial, 69 women, *evidence graded low;* RR 0.29, 95% CI 0.11 to 0.80, one trial, 69 women), and **frequency of leg cramps**: 50% reduction in number of leg cramps after treatment (RR 1.42, 95% CI 1.09 to 1.86, one trial, 86 women, *evidence graded low*). The outcomes that showed no difference were: **frequency of leg cramps** during two weeks of treatment (mean difference (MD) 1.80, 95% CI -1.32 to 4.92, one trial, 38 women, *evidence graded low*); **frequency of leg cramps** after treatment: daily, every other day, and once a week (RR 1.20, 95% CI 0.45 to 3.21, one trial, 69 women; RR 0.44, 95% CI 0.12 to 1.57, one trial, 69 women; RR 1.54, 95% CI 0.62 to 3.87, one trial, 69 women).

Evidence about whether magnesium supplements reduced the **intensity of pain** was inconclusive, with two studies showing that it may slightly reduce pain, while one showed no difference. There were no differences in the experience of **side effects** (including nausea, flatulence, diarrhoea and intestinal air) between pregnant women receiving magnesium compared with placebo/no treatment.

Oral calcium versus no treatment

A greater proportion of women receiving calcium supplements experienced no leg cramps after treatment than those receiving no treatment (**frequency of leg cramps** after treatment: never RR 8.59, 95% CI 1.19 to 62.07, one study, 43 women, *evidence graded very low*). There was no difference between groups for a **composite outcome (intensity and frequency)** for partial improvement (RR 0.64, 95% CI 0.36 to 1.15, one trial, 42 women); however, the same trial showed a greater proportion of women experiencing no leg cramps after treatment with calcium compared with no treatment (RR 5.50, 95% CI 1.38 to 21.86).

Other secondary outcomes, including **side effects**, were not reported.

Oral vitamin B versus no treatment

Frequency of leg cramps was not reported in the one included trial. According to a **composite outcome (frequency and intensity)**, more women receiving vitamin B fully recovered compared with those receiving no treatment (RR 7.50, 95% CI 1.95 to 28.81). Those women receiving no treatment were more likely to experience a partial improvement in the intensity and frequency of leg cramps than those taking vitamin B (RR 0.29, 95% CI 0.11 to 0.73, one trial, 42 women), or to see no change in their condition. However, these results are based on one small study with design limitations.

Other secondary outcomes, including **side effects**, were not reported.

Oral calcium versus oral vitamin C

There was no difference in the **frequency of leg cramps** after treatment with calcium versus vitamin C (RR 1.33, 95% CI 0.53 to 3.38, one study, 60 women, *evidence graded very low*). Other outcomes, including**side effects**, were not reported.

Authors' conclusions

It is unclear from the evidence reviewed whether any of the interventions (oral magnesium, oral calcium, oral vitamin B or oral vitamin C) provide an effective treatment for leg cramps. This is primarily due to outcomes being measured and reported in different, incomparable ways, and design limitations compromising the quality of the evidence (the level of evidence was graded *low* or *very low*). This was mainly due to poor study design and trials being too small to address the question satisfactorily.

Adverse outcomes were not reported, other than side effects for magnesium versus placebo/no treatment. It is therefore not possible to assess the safety of these interventions.

The inconsistency in the measurement and reporting of outcomes, meant that data could not be pooled, meta-analyses could not be carried out, and comparisons between studies are difficult.

The review only identified trials of oral interventions (magnesium, calcium, vitamin B or vitamin C) to treat leg cramps in pregnancy. None of the trials considered non-drug therapies, for example, muscle stretching, massage, relaxation, heat therapy, and dorsiflexion of the foot. This limits the completeness and applicability of the evidence.

Standardised measures for assessing the frequency, intensity and duration of leg cramps to be used in large well-conducted randomised controlled trials are needed to answer this question. Trials of non-drug therapies are also needed.

PLAIN LANGUAGE SUMMARY

Interventions for leg cramps during pregnancy

Leg cramps are experienced as sudden, intense involuntary contractions of the leg muscles. They are a common problem in pregnancy, especially in the third trimester. They are painful and can interfere with daily activities, disrupt sleep, and reduce quality of life. Various interventions have been used during pregnancy to treat leg cramps, including drug, electrolyte (magnesium, calcium, sodium) and vitamin therapies, and non-drug therapies such as muscle stretching. The goal of this review was to find out what is effective and safe for treating leg cramps during pregnancy.

We included six randomised controlled studies, with a total of 390 women who were 14 to 36 weeks pregnant, comparing either magnesium, calcium or vitamin B with placebo or no treatment, and comparing vitamin C with calcium. All treatments were given as tablets to be chewed or swallowed.

Magnesium supplements did not consistently reduce how often women experienced leg cramps when compared with placebo or no treatment. Studies measured this in different ways, sometimes showing that magnesium helped reduce the number of leg cramps but sometimes showing that it made no difference. Likewise, evidence about whether magnesium reduced the intensity of pain was inconclusive with one study showing a reduction while others showed no difference. There was no difference in the experience of side effects, such as nausea and diarrhoea.

A greater proportion of women receiving calcium experienced no leg cramps after treatment compared to women who did not receive any treatment, however another measure of improvement showed no difference between the groups.

More women who received vitamin B supplements fully recovered compared with those women receiving no treatment; however these results were from a small sample within a study with design limitations.

The frequency of leg cramps was no different between women treated with calcium and those treated with vitamin C.

The level of evidence was graded low or very low. This was mainly due to the small sample size of studies and poor study design. Two studies were well-conducted and reported. The other four had design limitations: women were not allocated to different treatment groups in the best way in several studies, and in two studies women knew whether they were receiving treatment or not. Adverse effects such as any effect of the treatment on pregnancy complications, labour and the baby were not reported. Several of the studies focused mainly on serum calcium and magnesium levels. The frequency and intensity of cramps and the duration of pain were not reported in a consistent way and often information was lacking on how they were measured, either during treatment, at the end of treatment or after treatment had stopped.

It is not clear from the evidence reviewed whether any of the oral interventions (magnesium, calcium, vitamin B or vitamin C) provide an effective and safe treatment for leg cramps in pregnancy. Supplements may have different effects depending on women's usual intake of these substances. No trials considered therapies such as muscle stretching, massage, relaxation or heat therapy.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Oral magnesium compared with placebo/no treatment for treating leg cramps in pregnancy

Patient or population: treating leg cramps in pregnancy
Settings: outpatient clinics in Norway, Sweden and Thailand
Intervention: oral magnesium
Comparison: placebo/no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo/no treatment	oral magnesium				
Frequency of leg cramps during treatment	The mean frequency of leg cramps during treatment in the control group was 0	The mean frequency of leg cramps during treatment in the intervention group was 1.8 higher (1.32 lower to 4.92 higher)	-	38 (1 RCT)	⊕⊕◯◯ LOW [1]	
Frequency of leg cramps after treatment: never	Study population		RR 5.66 (1.35 to 23.68)	69 (1 RCT)	⊕⊕◯◯ LOW [2,3]	
	57 per 1000	323 per 1000 (77 to 1000)				
	Moderate					
	57 per 1000	323 per 1000 (77 to 1000)				
Frequency: 50% reduction in number of leg cramps	Study population		RR 1.42 (1.09 to 1.86)	86 (1 RCT)	⊕⊕◯◯ LOW [4,5]	
	605 per 1000	859 per 1000 (659 to 1000)				

	Moderate				
	605 per 1000	859 per 1000 (659 to 1000)			
Intensity of pain during treatment: mean total scale points	The mean intensity of pain during treatment: mean total scale points in the control group was 0	The mean intensity of pain during treatment: mean total scale points in the intervention group was 1.8 higher (3.1 lower to 6.7 higher)	-	38 (1 RCT)	⊕⊕◯◯ LOW [1]
Intensity of pain: 50% reduction in pain score	Study population		RR 1.43 (0.99 to 2.06)	86 (1 RCT)	⊕◯◯◯ VERY LOW [1,4]
	488 per 1000	698 per 1000 (483 to 1000)			
	Moderate				
	488 per 1000	698 per 1000 (484 to 1000)			
Intensity of pain: visual analogue scale	The mean intensity of pain: visual analogue scale in the control group was 0	The mean intensity of pain: visual analogue scale in the intervention group was 17.5 lower (34.68 lower to 0.32 lower)	-	69 (1 RCT)	⊕⊕◯◯ LOW [2,5]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1]Wide CI crossing the line of no effect and small sample size.
[2]Design limitations.
[3]Few events and small sample size.
[4]Outcome is assessed using an arbitrary cut-off.
[5]Small sample size.

BACKGROUND

Description of the condition

Leg cramps in pregnancy are a common problem characterised by sudden, intense, painful, and involuntary contractions of the leg muscles in pregnant women not experiencing any leg cramps secondary to another other disease (e.g. amyotrophic lateral sclerosis, hypothyroidism, restless legs syndrome), receiving medication (e.g. diuretics), or undergoing haemodialysis (Allen 2012; Miller 2005; Young 2009). They are different from restless legs syndrome, an involuntary movement in legs without muscle contractions or pain (Allen 2003; Allen 2012), although both conditions can occur in pregnant women (Hensley 2009). Up to 30% to 50% of pregnant women suffer from leg cramps, especially in the third trimester. Almost two-thirds of these women experience leg cramps twice per week and they can occur at any time, particularly at night (Sohrabvand 2009). Unfortunately, the aetiology and the precise mechanism of leg cramps in pregnancy is still unclear. It is possible that they are associated with metabolic disorders in pregnancy, inactivity or excessive exercise, electrolyte imbalances (e.g. magnesium, calcium, and sodium) and vitamin (E and D) deficiency (Miller 2005; Page 1953; Parisi 2003; Young 2009). One possible pathophysiological explanation is that leg cramps are caused by lower motor neurons with hyperactive, high-frequency, involuntary nerve spontaneous discharge (Allen 2012; Miller 2005; Minetto 2013). To date, there is no guideline to clarify the diagnostic criteria of leg cramps in pregnancy, but clinical history, physical examination and laboratory tests are useful (McGee 1990; Miller 2005; Shaker 2005). In most cases, leg cramps only last for seconds, but in severe cases, leg cramps in pregnancy will last for minutes with severe pain, which can affect daily activities, limit exercise and performance, cause sleep disturbance and reduce the quality of life (Allen 2012; Hertz 1992; Soares 2006). Leg cramps have been included in sleep-related movement disorders (Merlino 2012). For pregnant women, leg cramps overnight can cause sleep disorders such as sleep loss and insomnia, which may affect the outcome of labour including the length of labour and mode of delivery (Hensley 2009; Hertz 1992; Lee 2004; Mindell 2000). One prospective, observational study including 131 pregnant women, found that pregnant women sleeping less than six hours per night and those with a severe sleep problem were, respectively, 4.5 times and 5.2 times more likely to undergo a caesarean delivery (Lee 2004). Leg cramps in pregnancy may also be related to depression which can increase placental corticotropin-releasing factor and initiate uterine contractions and cervical ripening, and might eventually cause labour difficulty, fetus hypoxia and increased risks of neonatal asphyxia and postpartum haemorrhage (Dayan 2002; Hickey 1995; Marcus 2003; Rondo 2003).

Description of the intervention

A number of interventions are available for leg cramps in pregnancy. The most commonly used can be divided into two categories: drug/electrolyte/vitamin therapies and non-drug therapies. Historically, quinine and its derivatives were the effective mainstay therapy for idiopathic muscle cramps, including leg cramps in pregnancy (Katzberg 2010). Quinine is effective in reducing the number and intensity of cramps (El-Tawil 2010; Man-Son-Hing 1998). Unfortunately, quinine is associated with many severe side effects, such as visual toxicity, auditory toxicity (e.g. hearing loss), cardiotoxicity, fetal teratogenicity (e.g. central nervous system, limb, facial and cardiac defects, optic nerve hypoplasia and deafness), gastrointestinal symptoms, and renal impairment (Langford 2003; Nishimura 1976; Pedersen 1985). Because of these serious adverse effects, multiple drug regulatory agencies have banned the use of quinine for muscle cramps (ADRAC 2002; FDA 2006; Medsafe 2007). Other commonly used drug/electrolyte/vitamin therapies include magnesium, calcium, sodium, vitamins (vitamin E, vitamin D) supplement and pycnogenol (Garrison 2012; Hammar 1987; Kohama 2006; Miller 2005; Nygaard 2008; Page 1953). In addition, one study also found anticonvulsants such as gabapentin were helpful for leg cramps (Serrao 2000). A lot of research has been done with these drug therapies, however, there are still no consistent conclusions for treating leg cramps in pregnancy. Non-drug therapies commonly used in treating acute cramps and preventing cramps include muscle stretching, massage, relaxation, heat therapy and dorsiflexion of the foot (Blyton 2012; Kanaan 2001; Miller 2005). Muscle stretching is a simple intervention and is suggested as the first line treatment in some studies (McGee 1990; Miller 2005). However, the effectiveness and safety of all therapies are not known.

How the intervention might work

Different interventions work in different ways. Quinine increases the refractory period of muscle and reduces the excitability of the motor end plate, thereby reducing its response to repetitive stimulation, nerve stimulation and acetylcholine, resulting in suppression of muscle cramps (El-Tawil 2010; Goodman 2001; Harvey 1939). Magnesium deficiency increases neuronal excitability and enhances neuromuscular transmission with muscle cramps as it has a curariform action on the neuromuscular junction and is associated with the release of acetylcholine from motor nerve terminals. (Wacker 1968). Hence, magnesium supplementation may suppress excitable tissue and suppress muscle cramps (Frusso 1999; Garrison 2012). However, the mechanism of many other interventions for leg cramps in pregnancy is unclear.

Why it is important to do this review

Leg cramps in pregnancy are a common problem, with the potential for adverse effects on the mother and baby. Other than quinine, which is not recommended in pregnancy, the effectiveness and safety of interventions for this problem have not been addressed (Allen 2012; El-Tawil 2010; Hensley 2009; Lee 2004). Five Cochrane reviews have investigated muscle cramps (including one previous review by Young 2002, which looked at interventions for leg cramps in pregnancy - the topic of our review). One review of non-drug therapies for lower limb muscle cramps did not focus on pregnant women (Blyton 2012). The Garrison 2012 review looked at magnesium for muscle cramps and carried out subgroup analysis on pregnant women but only compared placebo with no treatment. Another review assessed all interventions for muscle cramps in amyotrophic lateral sclerosis, but pregnancy-associated leg cramps were excluded (Baldinger 2012). In contrast, the Cochrane review by Young 2002 looked at interventions for leg cramps in pregnancy but there have since been new studies published in this area. Consequently, we prepared a protocol (Zhou 2013) for a new review team to prepare an updated Cochrane review on this topic.

A Cochrane review by El-Tawil 2010 focused on quinine and found it could significantly reduce the number and intensity of cramps in the general population, but was associated with significant gastrointestinal symptoms, haematological and cardiac toxicity events and fatal adverse effects. Quinine isexcluded from our review because of its known adverse effects. Magnesium and non-drug therapies are included in our review as we want to find the most effective intervention. In addition, other common therapies (e.g. calcium, sodium, various vitamins) still need to be evaluated.

OBJECTIVES

To assess the effectiveness and safety of different interventions for treating leg cramps in pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of any intervention (except for quinine *see* Background) for treatment of leg cramps in pregnancy. Studies for prevention of leg cramps in pregnancy were excluded. Cluster-randomised studies were considered as mentioned in the Unit of analysis issues. Quasi-RCTs were excluded due to obvious selection bias. Cross-over studies were also excluded.

Types of participants

Pregnant women who were experiencing leg cramps in pregnancy. However, pregnant women with leg cramps secondary to another disease (e.g. amyotrophic lateral sclerosis, hypothyroidism), receiving medication (e.g. diuretics), undergoing haemodialysis and pregnant women with restless legs syndrome were excluded.

Types of interventions

We included all therapeutic interventions for leg cramps in pregnancy, including:

1. drug/electrolyte/vitamin therapies, for example, calcium salts, magnesium salts, sodium salts, vitamins (vitamin D, vitamin E), and mineral supplements compared with placebo, no treatment or other treatment. We planned to exclude any trials of quinine, for its known adverse effects (teratogenicity);
2. non-drug therapies, for example, muscle stretching, massage, relaxation, heat therapy, dorsiflexion of the foot compared with placebo, no treatment or other treatment.

Types of outcome measures

Primary outcomes

Frequency of leg cramps. For example, measured as the number of leg cramps per week.

Secondary outcomes

1. Intensity of leg cramps. For example, level of pain intensity measured by validated instruments.
2. Duration of leg cramps. For example, measured by seconds per leg cramp.
3. Composite outcome: symptoms of leg cramps, including two or more of: frequency, pain intensity or duration of leg cramps (not prespecified).
4. Adverse outcomes:
   i) maternal side effects (e.g. nausea, vomiting, diarrhoea, constipation);
   ii) labour outcome (e.g. mode of birth);
   iii) pregnancy complications (e.g. hypertension, pre-eclampsia, antepartum haemorrhage);
   iv) pregnant outcomes: fetal death, including spontaneous abortion (before 20 weeks' gestation), preterm labour and stillbirth;
   v) neonatal outcomes: neonatal asphyxia, neonatal death: a baby death within 28 days of live birth;
   vi) congenital abnormalities (e.g. biochemical defects, genetic and chromosomal abnormalities).
5. Health-related quality of life, as measured by validated instruments.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 March 2015).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE, Embase and CINAHL, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted the third review author.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted the third review author. Data were entered into Review Manager software (RevMan 2014) and checked for accuracy.

When information regarding any of the above was unclear, we planned to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

1. low risk of bias (any truly random process, e.g. random number table; computer random number generator);
2. high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
3. unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

1. low, high or unclear risk of bias for participants;
2. low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

1. low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

1. low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
2. high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
3. unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

1. low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
2. high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
3. unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessing the quality of the evidence using the GRADE approach

We assessed the quality of the evidence using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following outcomes for the main comparison (oral magnesium versus placebo/no treatment*),* and the primary outcome for other comparisons (oral calcium versus no treatment, oral vitamin B versus no treatment, and oral calcium versus oral vitamin C).

1. Frequency of leg cramps, for example, measured as the number of leg cramps per week.
2. Intensity of leg cramps, for example, pain intensity measured by validated instruments.
3. Duration of leg cramps, for example, measured by seconds per leg cramp.
4. Composite outcome: symptoms of leg cramps, including two or more of: frequency, pain intensity or duration of leg cramps (not prespecified).
5. Maternal side effects (e.g. nausea, vomiting, diarrhoea, constipation).

We used GRADE profiler (GRADE 2014) to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for important outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

We used the mean difference if outcomes were measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

No cluster-randomised trials were identified for this review. Had we found any cluster-randomised trials, we would have included them along with the individually-randomised trials.Their sample sizes or standard errors would have been adjusted using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we had used ICCs from other sources, we would have reported this and conducted sensitivity analyses to investigate the effect of variation in the ICC. If we had identified both cluster-randomised trials and individually-randomised trials, we planned to synthesise the relevant information. We would have considered it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely.

Other unit of analysis issues

Multiple pregnancies studies

No trials focused on multiple pregnancies were identified for this version of the review. Had we included studies involving women with multiple pregnancies, we would have treated the infants as independent and noted effects of estimates of confidence intervals in the review.

Multi-arm studies

We included one multi-arm study (Sohrabvand 2006). We sought statistical advice on how to present the results of this study. The participants assigned to no treatment have been used as a comparison with magnesium, calcium and vitamin B, and appropriate cautions have been added to the results text.

Dealing with missing data

For included studies, we noted levels of attrition. In future updates, if more eligible studies are included, the impact of including studies with high levels of missing data in the overall assessment of treatment effect will be explored by using sensitivity analysis.
For all outcomes, analyses were carried out, as far as possible, on an intention-to-treat basis i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau², I² and Chi² statistics. We regarded heterogeneity as substantial if an I² was greater than 30% and either a Tau² was greater than zero, or there was a low P value (less than 0.10) in the Chi² test for heterogeneity. Had we identified substantial heterogeneity (above 30%), we planned to explore it by pre-specified subgroup analysis.

Assessment of reporting biases

In future updates, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014) but we did not combine data in meta-analysis due to insufficient data. In future updates of this review, we will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.
If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We did not combine data in meta-analysis due to insufficient data. However, in future updates, if we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We plan to undertake the following subgroup analyses by types of interventions:

1. gestational age at the end of the treatment: (1) 28 weeks or less; or (2) more than 28 weeks.

Subgroup analysis will be restricted to the primary outcome.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the χ^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

There were insufficient data in any one comparison to undertake sensitivity analysis to assess the effect of missing data or trial quality. In future updates of this review, if appropriate, we will carry out sensitivity analysis to explore the effects of trial quality assessed by allocation concealment and other 'Risk of bias' components, by omitting studies rated as inadequate for these components. We will also use sensitivity analysis to explore the effects of fixed-effect or random-effects analyses for outcomes with statistical heterogeneity and the effects of any assumptions made. Sensitivity analysis will be restricted to the primary outcome.

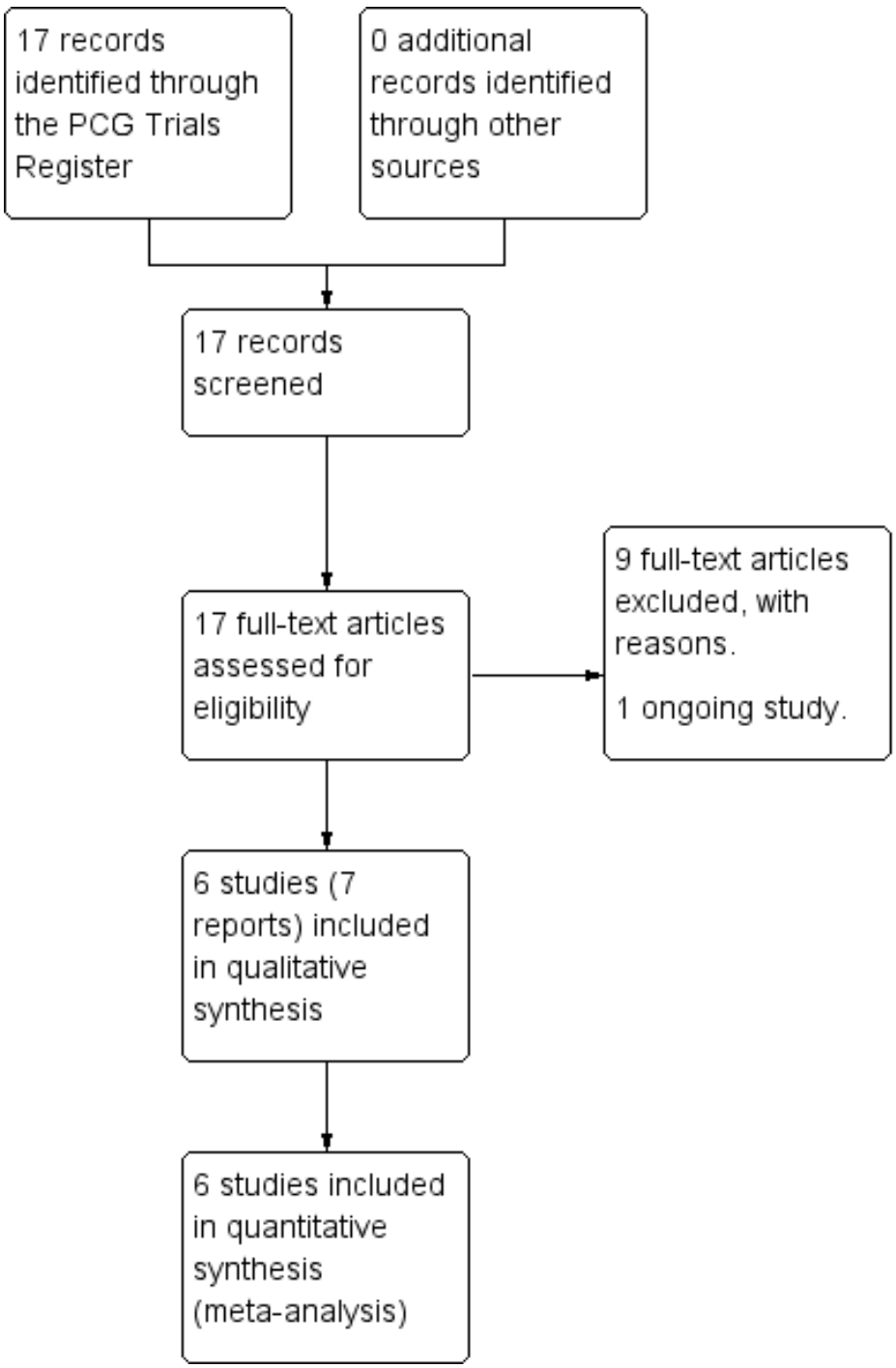
RESULTS

Description of studies

Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved 17 reports of 16 studies. *See*: Figure 1. Six studies (seven reports) were included in the review (Dahle 1995; Hammar 1981; Hammar 1987; Nygaard 2008; Sohrabvand 2006; Supakatisant 2012), nine studies were excluded (Griffith 1998; Kohama 2006; Mauss 1970; Mukherjee 1997; Odendaal 1974; Robinson 1947; Rougin 2012; Shahraki 2006; Thauvin 1992), and one study is ongoing (Mansouri 2013 - see Characteristics of ongoing studies).

Figure 1. Study flow diagram.



Included studies

Six studies (involving 390 women) were included in the review. See Characteristics of included studies.

Design

Five studies were two-arm randomised controlled trials. Three of these trials compared magnesium with placebo (Dahle 1995; Nygaard 2008; Supakatisant 2012), one compared calcium with no treatment (Hammar 1981), and one compared calcium with vitamin C (Hammar 1987). One study was a four-arm randomised controlled trial, in which women were allocated to receive calcium, magnesium, vitamin B or no treatment (Sohrabvand 2006). Two trials included an additional control group of pregnant women without leg cramps, who were not included in this review (Hammar 1981; Hammar 1987).

Sample sizes

The total number of women recruited to the trials was 390. Studies had a sample size ranging from 42 (Hammar 1981) to 86 (Supakatisant 2012).

Setting

Studies were carried out in Sweden (Dahle 1995; Hammar 1981; Hammar 1987), Norway (Nygaard 2008), Iran (Sohrabvand 2006), and Thailand (Supakatisant 2012). Recruitment and treatment took place in outpatient clinics (Dahle 1995; Nygaard 2008; Supakatisant 2012) or was not described (Hammar 1981; Hammar 1987; Sohrabvand 2006).

Participants

Pregnant women who were experiencing leg cramps were included in all studies. The inclusion criteria specified that women had experienced leg cramps at least twice a week (Hammar 1981; Nygaard 2008; Supakatisant 2012), for at least two weeks (Hammar 1981; Hammar 1987), and that they were painful (Nygaard 2008; Supakatisant 2012). Dahle 1995 and Sohrabvand 2006 did not specify the frequency, duration or intensity of leg cramps previously experienced by women eligible for the study. Women were eligible to participate if their gestation was 22 to 36 weeks (Dahle 1995), 18 to 36 weeks (Nygaard 2008), and 14 to 34 weeks (Supakatisant 2012).

Women were excluded from participation if they had already received treatment for leg cramps (Dahle 1995; Supakatisant 2012), and if they had concurrent medical conditions (Dahle 1995; Nygaard 2008; Supakatisant 2012). The inclusion and exclusion criteria were not described by Hammar 1981; Hammar 1987 and Sohrabvand 2006.

Interventions

All therapies were given orally.

The dose of magnesium was three chewable tablets of magnesium 120 mg (5 mmol) per day, one tablet in the morning and two each evening (primarily magnesium lactate and magnesium citrate) (Dahle 1995; Nygaard 2008), two tablets of magnesium 183.2 mg (7.5 mmol) per day (magnesium aspartate) (Sohrabvand 2006), and three tablets of 100 mg magnesium bisglycinate chelate per day (Supakatisant 2012). Treatment was for two weeks (Nygaard 2008; Sohrabvand 2006), three weeks (Dahle 1995), or four weeks (Supakatisant 2012).

Oral calcium preparations used were calcium gluconate, calcium lactate and calcium carbonate corresponding to a calcium dose of 1 g twice daily (Hammar 1981; Hammar 1987), and 500 mg calcium carbonate tablets once daily (Sohrabvand 2006). Treatment was for two weeks (Hammar 1981; Sohrabvand 2006), or three weeks (Hammar 1987).

The dose of vitamin C was 1 g twice daily for three weeks (Hammar 1987), and vitamin B was 100 mg of thiamine (vitamin B1) plus 40 mg of pyridoxine (vitamin B6) once daily for two weeks (Sohrabvand 2006).

Three studies used placebo tablets (Dahle 1995; Nygaard 2008; Supakatisant 2012), and two studies used no treatment as a comparison (Hammar 1981; Sohrabvand 2006). Comparisons between different treatments were made in two studies (Hammar 1987; Sohrabvand 2006).

Outcomes

Most studies measured biochemical outcomes, such as serum calcium and serum magnesium levels (Dahle 1995; Hammar 1981; Hammar 1987; Nygaard 2008), which are not of relevance to this review. Clinical outcomes were not reported in a consistent way and often there was a lack of information on how they had been measured. For example "frequency of leg cramps" (our primary outcome) was given as mean episodes during the treatment period (Nygaard 2008), number of cramps per week after treatment (Dahle 1995), 50% reduction in the number of leg cramps (Supakatisant 2012), and whether leg cramps had ceased after treatment. The outcome "intensity of leg cramps" (our second outcome) was given as a mean intensity of pain score during the treatment period (Nygaard 2008), 50% reduction in pain score of leg cramps (Supakatisant 2012), and the specific intensity pain score points (Dahle 1995). Only one study showed the outcome about "duration of the leg cramps", however, it was given as per-

sisting leg cramps after night-time (Dahle 1995). The "composite outcome" was reported as whether the frequency and intensity of leg cramps showed partial improvement or complete recovery (Sohrabvand 2006). Maternal side effects of nausea and diarrhoea were given (Nygaard 2008; Supakatisant 2012), however, other adverse events were not reported.

Studies measured the frequency and intensity of leg cramps at different time-points. Outcomes were assessed during treatment (Nygaard 2008; Supakatisant 2012), at the end of the treatment period (Dahle 1995; Hammar 1981; Hammar 1987), or in a time period after treatment has ceased (for example Sohrabvand 2006).

The authors of Sohrabvand 2006 and Supakatisant 2012 were contacted for additional information on the studies. A response was received from Sohrabvand 2006, with details of trial methodology and results not provided in the published report. At the time of writing, no response has been received from Supakatisant 2012.

Excluded studies

Nine studies identified by the search strategy were excluded from this review (see Characteristics of excluded studies). They were excluded because group allocation was not randomised (Mukherjee 1997; Robinson 1947; Shahraki 2006); a cross-over design was used (Mauss 1970); some women received more than one course of treatment, not necessarily the same treatment (Odendaal 1974); the pregnant women did not have leg cramps (Griffith 1998; Thauvin 1992), participants with leg cramps were combined with pregnant women experiencing other types of pain such as lower back pain and pelvic pain (Kohama 2006), or participants were not pregnant women (Rougin 2012).

Ongoing studies

One ongoing study was identified (Mansouri 2013, see Characteristics of ongoing studies). This is a three-arm randomised controlled trial, comparing vitamin D versus calcium plus vitamin D versus placebo for treating leg cramps in pregnant women. We contacted the authors to ask if unpublished results could be provided to contribute to this review. At the time of writing, no response has been received.

Risk of bias in included studies

See Characteristics of included studies, 'Risk of bias' graph (Figure 2) and Risk of bias' summary (Figure 3).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

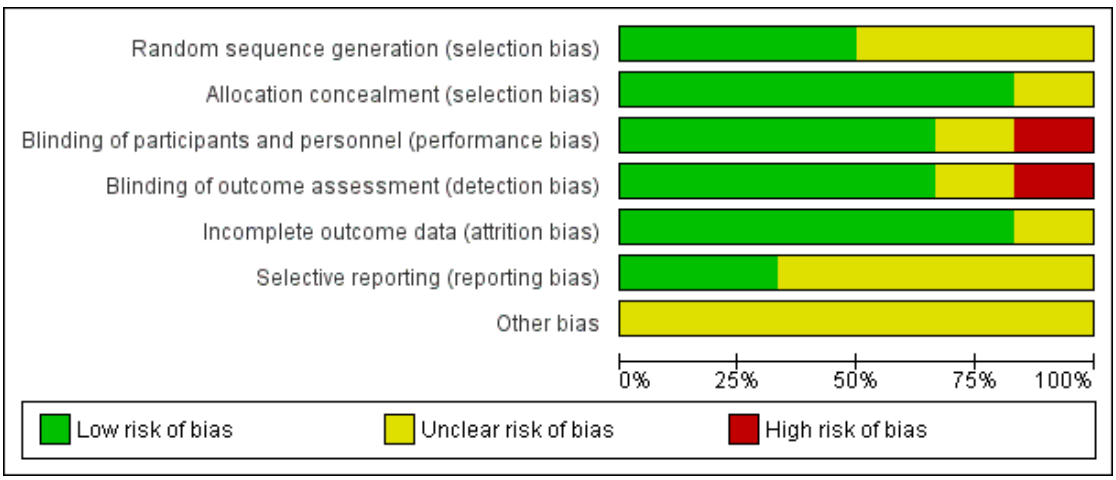
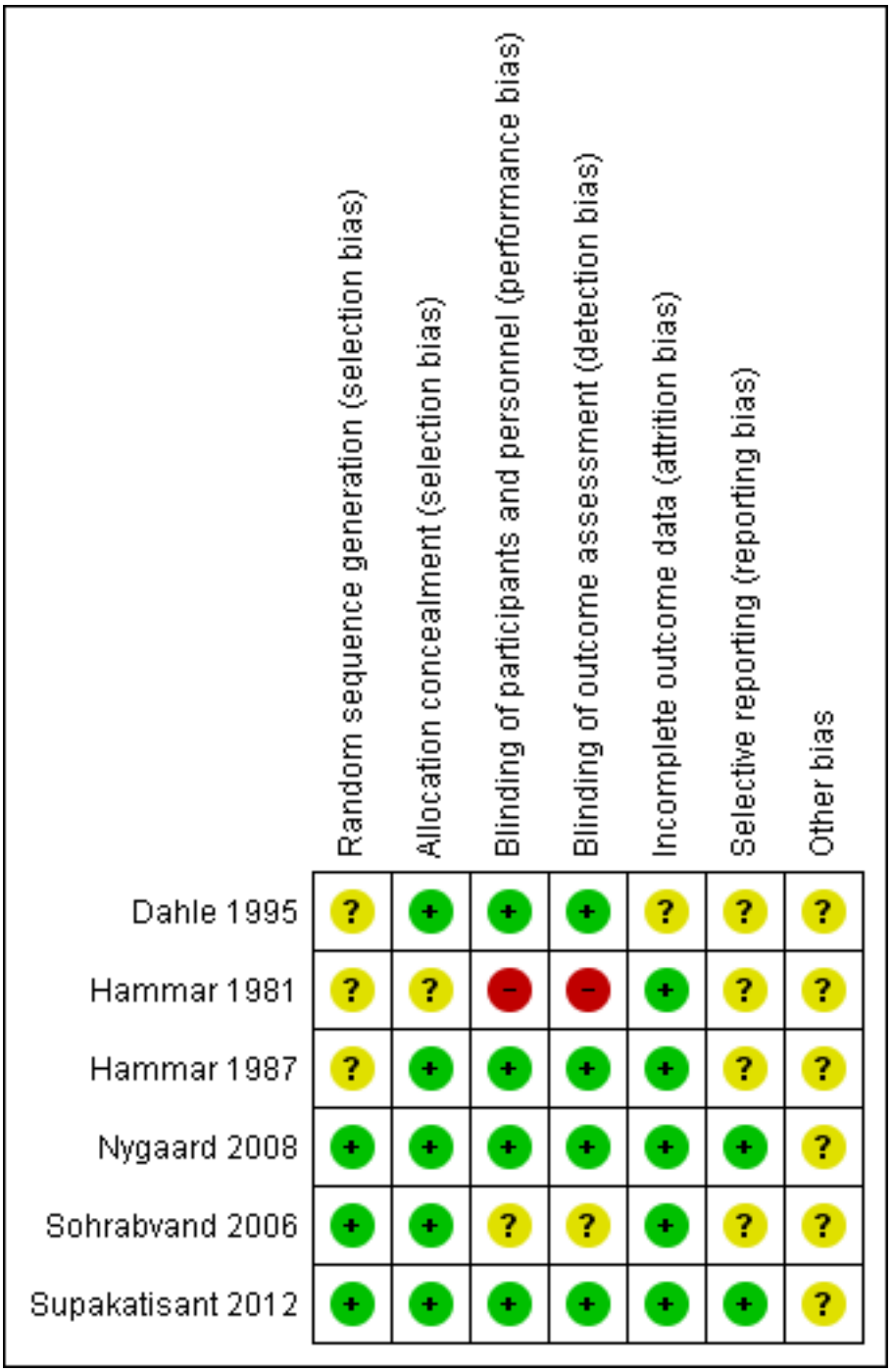


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In three studies, women were randomised using a random number table or randomisation programme to generate the sequence (low risk of bias, Nygaard 2008; Sohrabvand 2006; Supakatisant 2012). The remaining three studies state that pregnant women were randomly allocated, but give no description of the method (unclear risk of bias, Dahle 1995; Hammar 1981; Hammar 1987). Allocation concealment was achieved by using sequentially numbered drug containers of identical appearance in three studies (low risk of bias, Dahle 1995; Nygaard 2008; Supakatisant 2012), and numbered envelopes in one study (low risk of bias, Sohrabvand 2006). The code was not broken until women had completed the investigation, which suggests that allocation was concealed in Hammar 1987. The remaining study did not provide information on allocation concealment (unclear risk of bias, Hammar 1981).

Blinding

Four studies are described as double-blind, with the code not being broken until all women had completed the investigation (low risk of bias, Dahle 1995; Hammar 1987; Nygaard 2008; Supakatisant 2012). In one study, the control group received no treatment, so participants, personnel and outcome assessors were aware of whether or not they were receiving the intervention (high risk of bias, Hammar 1981). In another study, healthcare providers and the statistician were blinded, but women may have been aware of the group allocation as the timing and size of treatments was different (unclear risk of bias, Sohrabvand 2006).

Incomplete outcome data

Four women who were recruited by Dahle 1995 were subsequently excluded, the report does not state which group they had been allocated to, and the analysis is not intention-to-treat. It is unclear whether this would bias the results (unclear risk of bias). All women were accounted for in the other included studies (low risk of bias), however some studies had missing data. Results are presented for 84% of women recruited in Nygaard 2008 and for 93% of women in Supakatisant 2012. Both studies used intention-to-treat analyses.

Selective reporting

All outcomes pre-specified in the study protocols were reported in Nygaard 2008 and Supakatisant 2012 (low risk of bias). The other studies were assessed from published reports without access to the study protocol, so the level of reporting bias is unclear (Dahle 1995; Hammar 1981; Hammar 1987; Sohrabvand 2006).

Other potential sources of bias

One author declared a conflict of interest in Nygaard 2008, having contributed to developing the magnesium tablet used and received payment from the pharmaceutical company. Groups appear similar at baseline, where this information was given (Dahle 1995; Supakatisant 2012), however in most studies there was insufficient information to assess whether any other potential sources of bias existed (unclear risk of bias for all studies).

Effects of interventions

See: **Summary of findings for the main comparison** Oral magnesium compared with placebo/no treatment for treating leg cramps in pregnancy; **Summary of findings 2** Oral calcium compared with no treatment for treating leg cramps in pregnancy; **Summary of findings 3** Oral calcium compared with oral vitamin C for leg cramps in pregnancy

Oral magnesium versus placebo/no treatment

Primary outcomes

See Summary of findings for the main comparison.

Three studies (193 women) comparing oral magnesium with placebo or no treatment reported the **frequency of leg cramps**, however they did so in different ways, which could not be pooled in a meta-analysis. Some of these outcome measures showed reduced frequency of leg cramps in pregnant women receiving magnesium supplements compared with placebo or no treatment, others showed no differences between groups. Higher numbers of women who had received magnesium experienced no leg cramps after treatment than those in the placebo/no treatment group (frequency of leg cramps after treatment: never, risk ratio (RR) 5.66, 95% confidence interval (CI) 1.35 to 23.68, one trial, 69 women, *evidence graded low,* Analysis 1.3). Other measures that showed reduced frequency of leg cramps in pregnant women receiving magnesium supplements were frequency of leg cramps after treatment: twice a week (RR 0.29, 95% CI 0.11 to 0.80, one trial, 69 women, Analysis 1.2) and frequency of leg cramps: 50% reduction in number of leg cramps (RR 1.42, 95% CI 1.09 to 1.86, one trial, 86 women, *evidence graded low,* Analysis 1.4). Outcomes that showed no difference in the frequency of leg cramps between women who had received magnesium and those who had not were frequency of leg cramps during two weeks of treatment (mean difference (MD) 1.80, 95% CI -1.32 to 4.92, one trial, 38 women, *evidence graded low,* Analysis 1.1); frequency of leg cramps after treatment: daily (RR 1.20, 95% CI 0.45 to 3.21, one trial, 69 women, Analysis 1.2); frequency of leg cramps after treatment: every other day (RR

0.44, 95% CI 0.12 to 1.57, one trial, 69 women, Analysis 1.2); frequency of leg cramps after treatment: once a week (RR 1.54, 95% CI 0.62 to 3.87, one trial, 69 women, Analysis 1.2).

Secondary outcomes

The **intensity of pain** was also measured in a variety of ways, so data could not be pooled for this outcome. Two measures for this outcome may indicate that women receiving magnesium rate their pain as less intense than those receiving placebo (Intensity of pain: 50% reduction in pain score RR 1.43, 95% CI 0.99 to 2.06, one trial, 86 women, Analysis 1.6, *evidence graded very low;* Intensity of pain: visual analogue scale, MD -17.50, 95% CI -34.68 to -0.32, one trial, 69 women, *evidence graded low,* Analysis 1.7). However, one measure failed to show differences in the intensity of pain between those taking magnesium and placebo or no treatment (Intensity of pain during treatment: mean total scale points MD 1.80, 95% CI -3.10 to 6.70, one trial, 38 women, Analysis 1.5, *evidence graded low*).

The results for **duration of leg cramps** in one study of 69 women suggest that women in the oral magnesium group may be less likely to have symptoms that persist after night-time cramps (duration: persisting symptoms after night-time cramps: always RR 0.23, 95% CI 0.05 to 0.98; sometimes RR 0.59, 95% CI 0.19 to 1.83, Analysis 1.8).

One trial reported a **composite outcome of intensity and frequency of leg cramps** (42 women, two arms of a four-arm trial, Sohrabvand 2006). There was no difference in the levels of partial improvement (decrease in intensity and frequency of leg cramps) or complete recovery between groups receiving oral magnesium and no treatment (partial improvement: RR 1.07, 95% CI 0.71 to 1.61; complete recovery: RR 3.00, 95% CI 0.68 to 13.20; Analysis 1.9). The 'no treatment' group in this trial has been used in this review as the comparison group in magnesium versus placebo/no treatment, calcium versus no treatment, and vitamin B versus no treatment, giving it disproportionate weight in the overall analysis, and warranting cautious interpretation.

No differences were observed in the occurrence of **side effects**, (including nausea, diarrhoea, flatulence and intestinal air) in the results from two trials (131 women), although these results could not be pooled due to the method of reporting (nausea: RR 1.83, 95% CI 0.75 to 4.51, one trial, 86 women; diarrhoea: RR 6.00, 95% CI 0.75 to 47.76, one trial, 86 women; any side effect (including nausea and diarrhoea): RR 0.96, 95% CI 0.36 to 2.52, one trial, 45 women, Analysis 1.10).

Other secondary outcomes (**adverse outcomes** including pregnancy complications, and **health-related quality of life**) were not reported in the included studies.

Oral calcium versus no treatment

Primary outcomes

See Summary of findings 2.

The results of one study (43 women) contributed to this comparison, and showed that a greater proportion of women receiving oral calcium supplements experienced no leg cramps after treatment than those receiving no treatment (**frequency of leg cramps** after treatment: never: RR 8.59, 95% CI 1.19 to 62.07, *evidence graded very low,* Analysis 2.1). See 'Risk of bias' table for Hammar 1981).

Secondary outcomes

There was no difference in the levels of partial improvement (decrease in the **composite outcome of intensity and frequency of leg cramps**) between groups receiving oral calcium versus no treatment (RR 0.64, 95% CI 0.36 to 1.15, one trial, 42 women, Analysis 2.2), however this same trial showed a greater proportion of women experiencing no leg cramps after treatment with calcium compared with no treatment (RR 5.50, 95% CI 1.38 to 21.86, Analysis 2.2). These results are from a four-arm trial (Sohrabvand 2006). In this review, the 'no treatment' group has been used as the comparison group for oral magnesium versus placebo/no treatment, oral calcium versus no treatment, and oral vitamin B versus no treatment, giving it disproportionate weight in the overall analysis, thus interpretation of this result should be cautious.

Other secondary outcomes (**intensity of leg cramps, duration of leg cramps, adverse outcomes** including side effects and pregnancy complications, and **health-related quality of life**) were not reported in the included studies.

Oral vitamin B versus no treatment

Primary outcomes

The **frequency of leg cramps** was not reported in any included studies for this comparison.

Secondary outcomes

One four-arm trial reported on the **composite outcome (intensity and frequency of leg cramps)** for the comparison of oral vitamin B with no treatment (42 women. 21 of these women were in the 'no treatment' group, which has also been used in this review as the comparison group in oral magnesium versus placebo/no treatment and oral calcium versus no treatment giving these results undue weight, and therefore caution is advised in their interpretation). More women receiving oral vitamin B fully recovered compared with those allocated to no treatment (RR 7.50, 95% CI 1.95 to 28.81). Those women receiving no treatment were more likely to experience a partial improvement in the intensity and frequency of leg cramps than those taking vitamin B supplements (RR 0.29, 95% CI 0.11 to 0.73, one trial, 42 women, Analysis 3.1), or to see no change in their condition.

Other secondary outcomes (**intensity of leg cramps, duration of leg cramps, adverse outcomes** including side effects and pregnancy complications, and **health-related quality of life**) were not reported in the included study.

Oral calcium versus oral vitamin C

Primary outcomes

See Summary of findings 3.

One trial of 60 women compared these interventions. There was no difference in the outcome **frequency of leg cramps** after treatment: never (RR 1.33, 95% CI 0.53 to 3.38, *evidence graded very low*, Analysis 4.1).

Secondary outcomes

No secondary outcomes were reported in the included study (**intensity of leg cramps, duration of leg cramps, composite outcome for symptoms of leg cramps, adverse outcomes** including side effects and pregnancy complications, and **health-related quality of life**).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Oral calcium compared with no treatment for treating leg cramps in pregnancy

Patient or population: treating leg cramps in pregnancy
Settings: outpatient clinic in Sweden
Intervention: oral calcium
Comparison: no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk no treatment	Corresponding risk oral calcium				
Frequency of leg cramps after treatment: never	Study population		RR 8.59 (1.19 to 62.07)	43 (1 RCT)	⊕◯◯◯ VERY LOW [1,2]	
	48 per 1000	409 per 1000 (57 to 1000)				
	Moderate					
	48 per 1000	409 per 1000 (57 to 1000)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Serious design limitations.
[2]Few events and small sample size.

Oral calcium compared with oral vitamin C for leg cramps in pregnancy

Patient or population: leg cramps in pregnancy
Settings: outpatient clinic in Sweden
Intervention: oral calcium
Comparison: oral vitamin C

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	oral vitamin C	oral calcium				
Frequency of leg cramps after treatment: never	Study population		RR 1.33 (0.53 to 3.38)	60 (1 RCT)	⊕◯◯◯ VERY LOW [1,2]	
	200 per 1000	266 per 1000 (106 to 676)				
	Moderate					
	200 per 1000	266 per 1000 (106 to 676)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Design limitations.
[2]Wide CI crossing the line of no effect, few events and small sample size.

DISCUSSION

Summary of main results

We included six studies, with a total of 390 pregnant women (14 to 36 weeks) randomised. These trials contributed results to the comparison of oral magnesium, oral calcium or oral vitamin B with placebo or no treatment, and oral calcium with oral vitamin C. The level of evidence was graded *low* or *very low*, see Summary of findings for the main comparison; Summary of findings 2; and Summary of findings 3. This was mainly due to the small sample size of studies and poor study design. Outcomes were reported in different ways, precluding the pooling of results and the use of meta-analysis, and limiting the strength of our conclusions.

Oral magnesium was not consistently shown to reduce the frequency and intensity of leg cramps compared with placebo or no treatment. Some outcome measures showed reduced frequency of leg cramps in women randomised to receive magnesium, while others showed no differences between groups. There was no difference in the occurrence of side effects (including nausea, diahorrhoea, flatulence and intestinal air) between pregnant women receiving oral magnesium compared with placebo or no treatment.

Oral calcium supplements appeared to reduce leg cramps frequency in pregnancy for some outcome measures, while the other outcomes showed no difference. There was no consistent conclusion about it. Side effects were not reported in studies of this intervention.

Only one small sample and limited design study showed that oral vitamin B supplements may reduce the frequency and intensity (composite outcome) of leg cramps. However, frequency was not reported individually, and there were no data on side effects.

There was no difference in the frequency of leg cramps after treatment with oral calcium compared with oral vitamin C.

Overall completeness and applicability of evidence

The review only considers trials of interventions to treat leg cramps in pregnancy, not interventions to prevent leg cramps. This evidence is therefore not applicable to the population of pregnant women interested in avoiding this condition.

Supplements may have different effects depending on the baseline intake of the compounds, and pre-existing deficiencies. In different cultures, pregnant women consume different amounts of the dietary vitamins and minerals considered as interventions in this review, therefore treatment of leg cramps may vary depending on individual and cultural variables.

Several of the trials included in this review focused primarily on biochemical markers in the blood as indirect evidence of leg-cramp symptoms (Dahle 1995; Hammar 1981; Hammar 1987; Nygaard 2008). This objective may explain some of the inadequacies in the reporting of clinical data. The lack of reporting of adverse outcomes, such as maternal side effects, labour outcome, pregnancy complications, and neonatal outcomes, means that the safety of the interventions cannot be assessed.

Trials were not consistent in when they assessed the effects of treatment. Studies measured the frequency and intensity of leg cramps during treatment (Nygaard 2008; Supakatisant 2012), at the end of the treatment period (Dahle 1995; Hammar 1981; Hammar 1987), or in a time period after treatment has ceased (for example Sohrabvand 2006). Depending on how the treatment acts, these may show different effects.

The small number of included studies (six), and small sample sizes of those studies (42 to 86 women, 390 in total), mean that the evidence is incomplete and not generalisable.

No trials considered non-drug therapies, for example, muscle stretching, massage, relaxation, heat therapy, dorsiflexion of the foot compared with placebo, no treatment or other treatment.

Quality of the evidence

This review includes two well-conducted and reported trials, with no known design limitations (Nygaard 2008; Supakatisant 2012). The other included studies had design limitations. The descriptions of randomisation and allocation procedures were not optimal in three studies (Dahle 1995; Hammar 1981; Hammar 1987). It is unclear whether this is due to omissions in the reporting of the studies, or limitations of study design. Correspondance with the author of Sohrabvand 2006 revealed that, although the published report did not give details, randomisation and allocation were well-conducted. Two studies did not attempt to blind participants or clinicians to group allocation (Hammar 1981; Sohrabvand 2006). Women would have been aware of the intervention and this may have affected their perception or reporting of pain and side effects.

The level of evidence for oral magnesium versus placebo/no treatment was graded *low* (frequency of leg cramps during treatment, frequency of leg cramps after treatment: never, frequency: 50% reduction in number of leg cramps, intensity of pain during treatment: mean total scale points, intensity of pain: visual analogue scale) or *very low* (intensity of pain: 50% reduction in pain score) (Summary of findings for the main comparison). For oral calcium versus no treatment it was graded *very low* (frequency of leg cramps after treatment: never) (Summary of findings 2). No primary outcomes were reported for oral vitamin B versus no treatment, so a 'Summary of findings' table was not created. For oral vitamin C versus oral calcium, a grading of *very low* was made (frequency of leg cramps after treatment: never) (Summary of findings 3). All graded outcomes were downgraded for imprecision due to small sample size, and some also for wide confidence intervals. Several outcomes were downgraded for quality of evidence due to design limitations in the studies. Outcomes reporting 50% reduction were downgraded for indirectness, as they used an arbitrary cut-off for frequency and intensity of leg cramps.

The inconsistency in the measurement and reporting of frequency, intensity, and duration of pain, and the experience of side effects, meant that data could not be pooled, meta-analyses could not be carried out for these outcomes, and comparisons between studies are difficult.

Potential biases in the review process

One of the included studies was a four-arm trial, and the 'no treatment' group was used as the comparison group in oral magnesium versus placebo/no treatment, oral calcium versus no treatment, and oral vitamin B versus no treatment, giving it disproportionate weight in the overall analysis. This has been highlighted in the results, and appropriate caution has been applied in the interpretation of these results.

The assessment of risk of bias involves subjective judgements. This potential limitation is minimised by following the procedures in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), with review authors independently assessing studies and resolving any disagreement through discussion, and if required involving a third assessor in the decision.

Several trial authors were contacted with requests for additional data, in the hope that unpublished results might yield comparable outcomes. Additional information on methodology and results was received from Sohrabvand 2006. Mansouri 2013 replied that they were seeking to publish the results of their trial, and were unable to provide data at present. No response has yet been received from Supakatisant 2012.

Agreements and disagreements with other studies or reviews

This review disagrees with the previous version (Young 2002), which concluded that magnesium may have benefits for leg cramps in pregnancy, and calcium did not appear to have benefits, according to the limited evience.The conclusions of this review may alter in the future with evidence from more studies.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence is currently unclear and inconsistent. Evidence from these studies was too limited in quantity and quality to provide clinical direction for the use of oral magnesium, oral calcium, oral vitamin B or oral vitamin C for treating leg cramps in pregnancy. Adverse effects were also unclear in these studies, with side-effect data only available for the comparison of oral magnesium with placebo or no treatment. There was no evidence available to include in this review on other interventions, including non-drug therapies such as muscle stretching, massage, relaxation, heat therapy, or dorsiflexion.

It is difficult to provide accurate advice for pregnant women based on the evidence presented in this review. Current guidelines and other reviews often offer incomplete evidence, without comment on the quality of the evidence. It is not possible at present to identify, with confidence, safe and effective interventions for leg cramps in pregnancy.

Implications for research

The development of a standardised set of core outcomes for measuring the frequency, intensity and duration of leg cramps are needed for this area to be investigated. Well-conducted randomised controlled trials would then be able to evaluate interventions for treating leg cramps in pregnancy.

The safety of interventions should be assessed, by including analysis of adverse outcomes in the mother and baby in trial outcomes.

High-quality randomised controlled trials of non-drug therapies would also be a valuable addition to the field.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, the protocol for this review was commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Dahle 1995 *{published data only}*
Dahle LO, Berg G, Hammar M, Hurtig M, Larsson L. The effect of oral magnesium substitution on pregnancy-induced leg cramps. *American Journal of Obstetrics and Gynecology* 1995;**173**:175–80.

Hammar 1981 *{published data only}*
Hammar M, Larsson L, Tegler L. Calcium treatment of leg cramps in pregnancy. *Acta Obstetricia et Gynecologica Scandinavica* 1981;**60**:345–7.

Hammar 1987 *{published data only}*
Hammar M, Berg G, Solheim F, Larsson L. Calcium and magnesium status in pregnant women. A comparison between treatment with calcium and vitamin C in pregnant women with leg cramps. *International Journal of Vitamin and Nutrition Research* 1987;**57**:179–83.

Nygaard 2008 *{published data only}*
Nygaard IH, Valbo A, Pethick SV, Bohmer T. Does oral magnesium substitution relieve pregnancy-induced leg cramps?. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2008;**141**(1):23–6.

Sohrabvand 2006 *{published data only}*
Sohrabvand F, Shariat M, Haghollahi F. Vitamin B supplementation for leg cramps during pregnancy. *International Journal of Gynecology & Obstetrics* 2006;**95**(1): 48–9.

Supakatisant 2012 *{published data only}*
Phupong V. A randomized, double-blinded, placebo-controlled trial of oral magnesium for relief in pregnancy-induced leg cramps. Current Controlled Trials (http://www.controlled-trials.com/ISRCTN03989660) 2011 [accessed 31 January 2013].
* Supakatisant C, Phupong V. Oral magnesium for relief in pregnancy-induced leg cramps: a randomised controlled trial. *Maternal & Child Nutrition* 2015;**11**(2):139–45.

References to studies excluded from this review

Griffith 1998 *{published data only}*
Griffith EC, Crowther CA, Hiller JE, Wilson KJ, ACT Study Group. Leg cramps in pregnancy: ineffectiveness of calcium supplementation. 2nd Annual Congress of the Perinatal Society of Australia & New Zealand; 1998 March 30-April 4; Alice Springs, Australia. 1998:99.

Kohama 2006 *{published data only}*
Kohama T, Inoue M. Pycnogenol alleviates pain associated with pregnancy. *Phytotherapy Research* 2006;**20**(3):232–4.

Mauss 1970 *{published data only}*
Mauss HJ. Muscular cramp in the calf caused by pregnancy. Therapy in a blind study [Schwangerschaftsbedingte Wadenkrampfe. Therapie im Blindversuch.]. *Medizinische Welt* 1970;**36**:1570–1.

Mukherjee 1997 *{published data only}*
Mukherjee J, Jong A, Wu MY, Tsim YL. Leg cramps in pregnancy and calcium supplementation. *Acta Obstetricia et Gynecologica Scandinavica* 1997;**76**(167):89.

Odendaal 1974 *{published data only}*
Odendaal HJ. Calcium for the treatment of leg cramps during pregnancy [Kalsium vir die Behandeling van Beenkrampe tydens Swangerskap]. *South African Medical Journal* 1974;**48**:780–1.

Robinson 1947 *{published data only}*
Robinson M. Cramps in pregnancy. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1947;**54**:826–9.

Rougin 2012 *{published data only}*
Rougin M. Magnesium oxide monohydrate for nocturnal leg cramps (MgNLC); a prospective, randomized, double blind, placebo controlled clinical trial. ClinicalTrials.gov (http://clinicaltrials.gov/) [accessed 31 January 2014] 2012.

Shahraki 2006 *{published data only}*
Shahraki AD. Effects of vitamin E, calcium carbonate and milk of magnesium on muscular cramps in pregnant women. *Journal of Medical Sciences* 2006;**6**(6):979–83.

Thauvin 1992 *{published data only}*
Thauvin E, Fusselier M, Arnaud J, Faure H, Favier M, Coudray C, et al. Effects of multivitamin mineral supplement on zinc and copper status during pregnancy. *Biological Trace Element Research* 1992;**32**:405–14.

References to ongoing studies

Mansouri 2013 *{published data only}*
Mansouri A. The effect of vitamin D and calcium plus vitamin D for leg cramps in pregnant women: a randomised controlled trial. Iranian Registry of Clinical Trials (www.irct.ir) [accessed 24 March 2014] 2013.

Additional references

ADRAC 2002
Adverse Drug Reactions Advisory Committee. Quinine and profound thrombocytopenia. *Australian Adverse Drug Reactions Bulletin* 2002;**21**(3):10.

Allen 2003
Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J, et al. Restless legs syndrome: Diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Medicine* 2003;**4**(2):101–19.

Allen 2012
Allen RE, Kirby KA. Nocturnal leg cramps. *American Family Physician* 2012;**86**(4):350–5.

Baldinger 2012
Baldinger R, Katzberg HD, Weber M. Treatment for cramps in amyotrophic lateral sclerosis/motor neuron

disease. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: 10.1002/14651858.CD004157.pub2]

Blyton 2012
Blyton F, Chuter V, Walter KE, Burns J. Non-drug therapies for lower limb muscle cramps. *Cochrane Database of Systematic Reviews* 2012, Issue 1. [DOI: 10.1002/14651858.CD008496.pub2]

Dayan 2002
Dayan J, Creveuil C, Herlicoviez M, Herbel C, Baranger E, Savoye C, et al. Role of anxiety and depression in the onset of spontaneous preterm labor. *American Journal of Epidemiology* 2002;**155**:293–301.

El-Tawil 2010
El-Tawil S, Al Musa T, Valli H, Lunn MPT, El-Tawil T, Weber M. Quinine for muscle cramps. *Cochrane Database of Systematic Reviews* 2010, Issue 12. [DOI: 10.1002/14651858.CD005044.pub2]

FDA 2006
Food, Drug Administration. Quinine: important warning. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108799.htm [accessed 20 July 2008] 2006 11 Dec.

Frusso 1999
Frusso R, Zárate M, Augustovski F, Rubinstein A. Magnesium for the treatment of nocturnal leg cramps: a crossover randomized trial. *Journal of Family Practice* 1999; **48**(11):868–71.

Garrison 2012
Garrison SR, Allan GM, Sekhon RK, Musini VM, Khan KM. Magnesium for skeletal muscle cramps. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD009402.pub2]

Goodman 2001
Goodman L, Gilman A. *The Pharmacological Basis of Therapeutics*. 10th Edition. New York: McGraw-Hill, 2001.

GRADE 2014 [Computer program]
McMaster University. GRADEpro. [Computer program on www.gradepro.org]. Version 2015. McMaster University, 2014.

Harvey 1939
Harvey A. The mechanism of action of quinine in myotonia and myasthenia. *JAMA* 1939;**112**:1562–3.

Hensley 2009
Hensley JG. Leg cramps and restless legs syndrome during pregnancy. *Journal of Midwifery and Women's Health* 2009; **54**(3):211–8.

Hertz 1992
Hertz G, Fast A, Feinsilver SH, Feinsilver CL, Albertario H, Schulman, et al. Sleep in normal late pregnancy. Sleep 1992; Vol. 15, issue 3:246–51.

Hickey 1995
Hickey CA, Cliver SP, Goldenberg RL, McNeal SF, Hoffman HJ. Relationship of psychosocial status to low prenatal weight gain among nonobese black and white women delivering at term. *Obstetrics and Gynecology* 1995; **86**:177–83.

Higgins 2011
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Kanaan 2001
Kanaan N, Sawaya R. Nocturnal leg cramps. Clinically mysterious and painful--but manageable. *Geriatrics* 2001; **56**(6):39–42.

Katzberg 2010
Katzberg HD, Khan AH, So YT. Assessment: symptomatic treatment for muscle cramps (an evidence-based review): report of the therapeutics and technology assessment subcommittee of the American academy of neurology. *Neurology* 2010;**74**(8):691–6.

Langford 2003
Langford NJ, Good AM, Laing WJ, Bateman DN. Quinine intoxications reported to the Scottish Poisons Information Bureau 1997-2002: a continuing problem. British Journal of Clinical Pharmacology. United Kingdom: Blackwell Publishing Ltd, 2003; Vol. 56, issue 5:576–8.

Lee 2004
Lee KA, Gay CL. Sleep in late pregnancy predicts length of labor and type of delivery. *American Journal of Obstetrics and Gynecology* 2004;**191**(6):2041–6.

Man-Son-Hing 1998
Man-Son-Hing M, Wells G, Lau A. Quinine for nocturnal leg cramps a meta-analysis including unpublished data. Journal of General Internal Medicine. United States: Blackwell Publishing Inc., 1998; Vol. 13, issue 9:600–6.

Marcus 2003
Marcus SM, Flynn HA, Blow FC, Barry KL. Depressive symptoms among pregnant women screened in obstetrics settings. *Journal of Women's Health* 2003;**12**:373–80.

McGee 1990
McGee SR. Muscle cramps. *Archives of Internal Medicine* 1990;**150**:511–8.

Medsafe 2007
Medsafe Pharmacovigilance Team, New Zealand Medicines and Medical Devices Safety Authority. Quinine - not for leg cramps anymore. http://www.medsafe.govt.nz/profs/PUArticles/watchingbriefsNov07.htm Prescriber Update 2007; Vol. 28, issue 1:2–6.

Merlino 2012
Merlino G, Gigli GL. Sleep-related movement disorders. *Neurological Sciences* 2012;**33**(3):491–513.

Miller 2005
Millller TM, Layzer RB. Muscle cramps. *Muscle and Nerve* 2005;**32**(4):431–42.

Mindell 2000
Mindell JA, Jacobson BJ. Sleep disturbances during pregnancy. *Journal of Obstetric, Gynecologic, and Neonatal Nursing* 2000;**29**(6):590–7.

Minetto 2013
Minetto MA, Holobar A, Botter A, Farina D. Origin and development of muscle cramps. *Exercise and Sport Sciences Reviews* 2013;**41**(1):3–10.

Nishimura 1976
Nishimura H, Tanimura T. *Clinical aspects of the teratogenicity of drugs*. Excerpta Medica Amsterdam, 1976.

Page 1953
Page EW, Page EP. Leg cramps in pregnancy; etiology and treatment. *Obstetrics and Gynecology* 1953;**1**:94–100.

Parisi 2003
Parisi L, Pierelli F, Amabile G, Valente G, Calandriello E, Fattapposta F, et al. Muscular cramps: proposals for a new classification. *Acta Neurologica Scandinavica* 2003;**107**: 176–86.

Pedersen 1985
Pedersen KE, Madsen JL, Klitgaard NA. Effect of quinine on plasma digoxin concentration and renal digoxin clearance. Acta Medica Scandinavica. Sweden, 1985; Vol. 218, issue 2:229–32.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rondo 2003
Rondo PHC, Ferreira RF, Nogueira F, Ribeiro MCN, Lobert H, Artes R. Maternal psychological stress and distress as predictors of low birth weight, prematurity and intrauterine growth retardation. *European Journal of Clinical Nutrition* 2003;**57**:266–72.

Schunemann 2009
Schunemann HJ. GRADE: from grading the evidence to developing recommendations. A description of the system and a proposal regarding the transferability of the results of clinical research to clinical practice [GRADE: Von der Evidenz zur Empfehlung. Beschreibung des Systems und Losungsbeitrag zur Ubertragbarkeit von Studienergebnissen]. *Zeitschrift fur Evidenz, Fortbildung und Qualitat im Gesundheitswesen* 2009;**103**(6):391–400.

Serrao 2000
Serrao M, Rossi P, Cardinali P, Valente G, Parisi L, Pierelli F. Gabapentin treatment for muscle cramps: an open-label trial. *Clinical Neuropharmacology* 2000;**23**(1):45–9.

Shaker 2005
Shaker HK, Mackler L, Huber TE. What is the diagnostic approach to a patient with leg cramps?. *Journal of Family Practice* 2005;**54**:817–8.

Soares 2006
Soares CN, Murray BJ. Sleep disorders in women: clinical evidence and treatment strategies. *Psychiatric Clinics of North America* 2006;**29**(4):1095–113.

Sohrabvand 2009
Sohrabvand F, Karimi M. Frequency and predisposing factors of leg cramps in pregnancy: a prospective clinical trial. *Tehran University Medical Journal* 2009;**67**(9):661–4.

Wacker 1968
Wacker WE, Parisi AF. Magnesium metabolism. *New England Journal of Medicine* 1968;**278**(13):712–7.

Young 2009
Young G. Leg cramps. *Clinical Evidence* 2009;**03**:1113.

References to other published versions of this review

Young 2002
Young G, Jewell D. Interventions for leg cramps in pregnancy. *Cochrane Database of Systematic Reviews* 2002, Issue 1. [DOI: 10.1002/14651858.CD000121]

Zhou 2013
Zhou K, Xu L, Li W, Zhang J. Interventions for leg cramps in pregnancy. *Cochrane Database of Systematic Reviews* 2013, Issue 7. [DOI: 10.1002/14651858.CD010655]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Dahle 1995

Methods	2-arm randomised controlled trial.
Participants	Inclusion criteria: pregnant women complaining of leg cramps during pregnancy, at 22-36 weeks' gestation Exclusion criteria: with other pregnancy complications or intercurrent medical problems. Previous treatment had been given for leg cramps in the current pregnancy Setting: 2 prenatal care units in Sweden.
Interventions	Experimental intervention: oral magnesium 5 mmol (primarily magnesium lactate, magnesium citrate) chewable tablet. 1 tablet each morning, and 2 each evening, for 3 weeks (34 women) Comparison intervention: placebo (primarily sorbitol, fructose-dextrose) chewable tablet, same treatment regimen as intervention (35 women) Four women were randomised but did not complete the study and were excluded from analyses. It is not clear to which group they belonged
Outcomes	Leg cramps duration, frequency, diurnal variation, distress, and whether nocturnal cramps persisted the following day. Whether the condition improved, deteriorated, or remained unchanged and side effects. Serum calcium, serum magnesium, 24-hour urine calcium, magnesium and creatinine
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"patients were randomly allocated to either magnesium or placebo." However no description of the method of randomisation
Allocation concealment (selection bias)	Low risk	"A magnesium-placebo tablet batch of 90 numbered bottles was prepared by AC0 Lakemedel (Stockholm)...permitting blinded statistical analysis at the end of the study." Sequentially numbered drug containers of identical appearance
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Study Design:.....in a prospective, double-blind, randomized trial." Blinding of participants and key study personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...permitting blinded statistical analysis at the end of the study." No blinding of outcome assessment, but the outcome measurement is not likely to be

Dahle 1995 (*Continued*)

		influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 women were excluded. Reasons are given, e.g. premature labour, but it is not clear which group they were from. The analysis was not by intention-to-treat
Selective reporting (reporting bias)	Unclear risk	Assessed only from published report, with insufficient information to permit judgement
Other bias	Unclear risk	Groups appear to be similar at baseline. Insufficient information to assess whether another important risk of bias exists

Hammar 1981

Methods	2-arm randomised controlled trial (with an additional control group of pregnant women without cramps, not included in meta-analysis)
Participants	Inclusion criteria: pregnant women who had leg cramps occurring at least twice a week during the last fortnight Exclusion criteria: not described. Setting: Sweden. No further information.
Interventions	Experimental intervention: oral calcium preparation with calcium gluconate, calcium lactate and calcium carbonate corresponding to a calcium dose of 1 g twice daily for 2 weeks (21 women) Comparison intervention: no treatment (21 women).
Outcomes	Serum calcium concentrations. Frequency of cramps.
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Mentions "randomization", but no information on method.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. The effect of this is likely to vary by outcome. A standardised questionnaire was used to assess persistence of leg cramps, which may have been influenced by lack of blinding. Serum calcium levels are unlikely to have been affected by lack

Hammar 1981 (*Continued*)

		of blinding, however these are not included in the review
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women included in analyses (although symptoms are described for 22 women in treatment group, when only 21 were randomised)
Selective reporting (reporting bias)	Unclear risk	The focus of the study is on serum calcium concentrations. Assessed from published report without access to protocol, so reporting bias difficult to assess
Other bias	Unclear risk	Insufficient information to assess whether another important risk of bias exists

Hammar 1987

Methods	2-arm randomised controlled trial, with 13 additional controls without leg cramps (not included in analysis)
Participants	Describe setting: Sweden. Inclusion criteria: pregnant women who had experienced leg cramps for more than 2 weeks Exclusion criteria: not described
Interventions	Experimental intervention: oral calcium preparation containing calcium gluconate, calcium lactate and calcium carbonate corresponding to a calcium dose of 1 g twice daily for 3 weeks (30 women) Comparison intervention: vitamin C 1 g twice daily for 3 weeks (30 women)
Outcomes	Frequency of cramps, serum calcium, magnesium and albumin concentrations
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study states that it was "randomised", but there is no description of the method
Allocation concealment (selection bias)	Low risk	Not specifically described, but the code was not broken until all women had completed

Hammar 1987 (*Continued*)

		the investigation, which suggests that allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-blind, and the code was not broken until all women had completed the investigation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The code was not broken until all women had completed the investigation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women appear to be accounted for in the analysis.
Selective reporting (reporting bias)	Unclear risk	Assessed from published report, without protocol. Focus is on biochemical outcomes, but all prespecified outcomes appear to be reported
Other bias	Unclear risk	Insufficient information to assess whether another important risk of bias exists

Nygaard 2008

Methods	2-arm randomised controlled trial.
Participants	Setting: outpatients, Norway. Inclusion criteria: healthy pregnant women between 18 and 36 weeks of pregnancy suffering painful leg cramps, at least twice a week. Norwegian as first language Exclusion criteria: women with restless legs symptoms. Women with pregnancy complications or other medical diseases. Twin pregnancy, oedema, pre-eclampsia, magnesium supplements beyond the trial treatment
Interventions	Experimental intervention: 120 mg (5 mmol) oral magnesium citrate, magnesium lactate chewable tables. 1 tablet in the morning and 2 tablets in the evening, for 2 weeks. 23 women were randomised, 2 subsequently dropped out Control: chewable placebo tablets. 1 tablet in the morning and 2 tablets in the evening, for 2 weeks. 22 women were randomised, 5 dropped out
Outcomes	Serum magnesium and calcium, urine magnesium and magnesium-creatinine,leg cramp frequency and intensity. Side effects (nausea, flatulence, diarrhoea, intestinal air)
Notes	Clinical Trials.gov ID NCT00525317.

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

Nygaard 2008 (*Continued*)

Random sequence generation (selection bias)	Low risk	"The randomisation program was provided by Medstat Research AS." No further information on method of randomisation
Allocation concealment (selection bias)	Low risk	Sequentially numbered drug containers of identical appearance. Code was only broken after completion
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Code was only broken after completion.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Code was broken for statistical analyses.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 women dropped out of the trial (2 treatment group, 5 placebo), and an intention-to-treat analysis was carried out. The risk of bias is low for clinical outcomes. Laboratory specimens were lost, leaving results for 64% of women for some biochemical outcomes, however these data are not included in the review
Selective reporting (reporting bias)	Low risk	The study protocol is available (Clinical Trials.gov ID NCT00525317) and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Unclear risk	Conflict of interest declared: 1 author contributed to developing the magnesium tablet used and received payment from the pharmaceutical company

Sohrabvand 2006

Methods	4-arm randomised controlled trial.
Participants	Describe setting: Iran. Inclusion criteria: pregnant women. From 401 pregnant women, 217 (54.5%) had leg cramps with different intensity and frequency and amongst them 84 who had an acceptable nutrition and no associated medical problem and agreed to enter the trial were recruited and randomly assigned to the 4 groups Exclusion criteria: not described.
Interventions	Group 1: oral 500 mg calcium carbonate tablets (Tehran Chimie, Iran) once daily for 2 weeks. 21 women Group 2: oral 7.5 mmol magnesium aspartate (Magnesiocard; Verla, Germany) twice daily for 2 weeks. 21 women

Sohrabvand 2006 (*Continued*)

	Group 3: oral 100 mg of thiamine (vitamin B1) plus 40 mg of pyridoxine (vitamin B6) (Tehran Chimie, Iran) once daily for 2 weeks. 21 women Group 4: no treatment. 21 women.
Outcomes	Assessed after 4 weeks. A decrease in the intensity and frequency of muscle cramps was considered a relative improvement and a complete absence of muscle cramps was considered an absolute improvement
Notes	Helen West contacted the authors to check that participants had leg cramps at the point of randomisation. They confirmed that they did, and provided additional information on the methodology and results

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A random number table was used.
Allocation concealment (selection bias)	Low risk	A series of envelopes numbered from 1 to 84 had been prepared. Each patient was invited to pull out an envelope and was placed by the clinic secretary in 1 of the 4 groups
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The drugs were given in similar boxes to the participants, but since the timing and size of the tablets was different complete blinding was not possible. The healthcare providers and statistician were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The healthcare providers and statistician were blinded. Women self-reported on their symptoms, and may have been aware of their group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data appear to be presented for all women recruited.
Selective reporting (reporting bias)	Unclear risk	No information provided on whether outcomes were prespecified
Other bias	Unclear risk	Insufficient information available to assess whether another important risk of bias exists

Supakatisant 2012

Methods	2-arm randomised controlled trial.
Participants	Setting: antenatal care clinic at the Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand Inclusion criteria: pregnant women with leg cramps (defined as: sudden tonic or clonic involuntary contraction of the gastrocnemius muscle associated with severe pain). 14-34 weeks of gestation, having pregnancy-induced leg cramps at least twice a week Exclusion criteria: other medical disease, concurrent obstetrics complication, other prescriptions for leg cramps, history of magnesium allergy, pregnant women with multifetal gestation, subsequently developed pregnancy induced hypertension and preterm labour treated with tocolytic agent
Interventions	Experimental intervention: oral magnesium bisglycinate chelate (100 mg magnesium), 1 tablet, 3 times a day with meals, for 4 weeks. 43 women randomised (data for 41) Control: placebo, 1 tablet, 3 times a day with meals, for 4 weeks. 43 women randomised (data for 39)
Outcomes	50% reduction of number of leg cramps, 50% reduction of pain score of leg cramps. Side effects
Notes	ISRCTN0389660. HW contacted the authors on 23/3/15 to request additional data on frequency and intensity of leg cramps after treatment, and side effects

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table using a block-of-4 technique, generated by co-investigator who did not have patient contact
Allocation concealment (selection bias)	Low risk	Sequentially-numbered opaque plastic containers of identical size, shape and colour tablets
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both healthcare providers and women were masked to treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Women self-reported outcomes. The treatment assignment was not revealed until data collection was completed
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 women left the study because of personal reasons and other 3 women were lost to follow-up. 86 women were included in the intention-to-treat analysis by a 'worst-case' scenario

Supakatisant 2012 (*Continued*)

Selective reporting (reporting bias)	Low risk	Assessed from study protocol and published report, all prespecified outcomes reported
Other bias	Unclear risk	Baseline characteristics appear similar between groups, although possibly placebo group had less frequent but more severe leg cramps

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Griffith 1998	The method of randomisation was unclear. Not an intervention for leg cramps, the participants included pregnant women without leg cramps
Kohama 2006	This is not a randomised controlled trial, and included women with other types of pain (including lower back pain, hip joint pain and pelvic pain) in addition to leg cramps
Mauss 1970	Cross-over study, not a randomised controlled trial.
Mukherjee 1997	Quasi-randomised controlled trial (alternate allocation).
Odendaal 1974	Some women received more than 1 course of treatment, not necessarily the same treatment
Robinson 1947	Quasi-randomised controlled trial (alternate allocation).
Rougin 2012	The participants were not pregnant women.
Shahraki 2006	Quasi-randomised controlled trial (alternate allocation "The total number of samples was 120 persons, whose divided into 3 groups and each group was included 40 persons which were divided randomizly and turn of coming" p980)
Thauvin 1992	Not an intervention for leg cramps. The participants included pregnant women without leg cramps

Characteristics of ongoing studies *[ordered by study ID]*

Mansouri 2013

Trial name or title	The effect of vitamin D and calcium plus vitamin D for leg cramps in pregnant women: a randomised controlled trial
Methods	3-arm randomised controlled trial.

Mansouri 2013 (*Continued*)

Participants	Inclusion criteria: pregnant women, age 18-35, gestational age 25-30 weeks, having leg cramps at least twice a week, literate Exclusion criteria: known thyroid, cardio-vascular, diabetes or renal diseases; intake of calcium and vitamin D supplements during pregnancy; allergy history to studied drugs
Interventions	Experiemental intervention 1: vitamin D (1000 units) for 60 days Experiemental intervention 2: calcium-vitamin D tablets (300 mg calcium carbonate plus 1000 units vitamin D) for 60 days Control: placebo tablet for 60 days.
Outcomes	Number, duration and severity of leg cramps: before intervention, 4 and 8 weeks after intervention Sleep quality: before and after intervention (Pittsburgh Sleep Quality Index) delivery characteristics, anthropometric indicators: after delivery
Starting date	April 2013.
Contact information	amene_mansouri66@yahoo.com Tabriz University of Medical Sciences, East Azerbaijan, Islamis Republic of Iran
Notes	IRCT20133040810324N12 HW contacted the authors on 3/4/15 to request results.

DATA AND ANALYSES

Comparison 1. Oral magnesium versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of leg cramps during treatment	1	38	Mean Difference (IV, Fixed, 95% CI)	1.80 [-1.32, 4.92]
2 Frequency of leg cramps after treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Daily	1	69	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.45, 3.21]
2.2 Every other day	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.12, 1.57]
2.3 Twice a week	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.11, 0.80]
2.4 Once a week	1	69	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.62, 3.87]
3 Frequency of leg cramps after treatment: never	1	69	Risk Ratio (M-H, Fixed, 95% CI)	5.66 [1.35, 23.68]
4 Frequency: 50% reduction in number of leg cramps	1	86	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.09, 1.86]
5 Intensity of pain during treatment: mean total scale points	1	38	Mean Difference (IV, Fixed, 95% CI)	1.80 [-3.10, 6.70]
6 Intensity of pain: 50% reduction in pain score	1	86	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.99, 2.06]
7 Intensity of pain: visual analogue scale	1	69	Mean Difference (IV, Fixed, 95% CI)	-17.50 [-34.68, -0.32]
8 Duration: persisting symptoms after night-time cramps	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Always	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.05, 0.98]
8.2 Sometimes	1	69	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.19, 1.83]
9 Composite outcome: symptoms of leg cramps (intensity and frequency)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Partial improvement: decrease in intensity and frequency	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.71, 1.61]
9.2 Complete recovery: no leg cramps after treatment	1	42	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.68, 13.20]
10 Side effects	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Nausea	1	86	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.75, 4.51]
10.2 Diarrhoea	1	86	Risk Ratio (M-H, Fixed, 95% CI)	6.0 [0.75, 47.76]
10.3 Any side effect (including nausea, flatulence, diarrhoea and intestinal air)	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.36, 2.52]

Comparison 2. Oral calcium versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of leg cramps after treatment: never	1	43	Risk Ratio (M-H, Fixed, 95% CI)	8.59 [1.19, 62.07]
2 Composite outcome: symptoms of leg cramps (intensity and frequency)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Partial improvement: decrease in intensity and frequency	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.36, 1.15]
2.2 Complete recovery: no leg cramps after treatment	1	42	Risk Ratio (M-H, Fixed, 95% CI)	5.5 [1.38, 21.86]

Comparison 3. Oral vitamin B versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Composite outcome: symptoms of leg cramps (intensity and frequency)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Partial improvement: decrease in intensity and frequency	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.11, 0.73]
1.2 Complete recovery: no leg cramps after treatment	1	42	Risk Ratio (M-H, Fixed, 95% CI)	7.5 [1.95, 28.81]

Comparison 4. Oral calcium versus oral vitamin C

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of leg cramps after treatment: never	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.53, 3.38]

CONTRIBUTIONS OF AUTHORS

Kunyan Zhou and Helen West assessed studies for inclusion, assessed risk of bias and extracted data. Helen West conducted the analysis and wrote the results and abstract. Kunyan Zhou and Helen West wrote the discussion and conclusions. Liangzhi Xu gave proposals for the review. Kunyan Zhou drafted the protocol, Wenjuan Li and Jing Zhang amended the protocol, Liangzhi Xu gave proposals for the protocol.

DECLARATIONS OF INTEREST

Kunyan Zhou: None known.

Helen M West is employed on an NIHR grant paid to the University of Liverpool. The funder has no influence on the content or conclusions of the reviews

Jing Zhang: None known.

Liangzhi Xu: None known.

Wenjuan Li: None known.

SOURCES OF SUPPORT

Internal sources

- (HW) Cochrane Pregnancy and Childbirth Group, Department of Women's and Children's Health, The University of Liverpool, Liverpool, UK.

External sources

- UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The secondary outcome "Composite outcome: symptoms of leg cramps, including two or more of: frequency, pain intensity or duration of leg cramps" was not prespecified, and has been added.

The outcomes were changed from specifying the measure to be used, to giving that measure as an example, so that other measures could be accommodated in the review,

1. "Frequency of leg cramps. Measured as the number of leg cramps per week" was changed to "Frequency of leg cramps. For example, measured as the number of leg cramps per week."

2. "Intensity of leg cramps. Level of pain intensity measured by validated instruments" was changed to "Intensity of leg cramps. For example, level of pain intensity measured by validated instruments".

3. "Duration of leg cramps. For example measured by seconds per leg cramp" was changed to "Duration of leg cramps. For example, measured by seconds per leg cramp".

Comparison of treatments with "other treatment" in addition to no treatment and placebo has been added.

Clarification that studies of prevention of leg cramps in pregnancy have been excluded has been added to "Types of studies", and the word "treatment" has been added to the "Objectives".

Methods for use of GRADE and producing 'Summary of findings' tables have been added to the review.

The 'Summary of findings' table is restricted to 7 lines for each comparison. The outcomes in this review were measured in a variety of ways. A selection from the prespecified outcomes therefore had to be made to fit this requirement. Frequency of leg cramps and intensity of leg cramps are presented. Duration, composite symptoms, and side effects are not included.

Planned subgroups were not listed correctly in the protocol. They have therefore been removed, and a subgroup for future versions of this review has been added.

Helen West has been added as an author since the protocol was published.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Ascorbic Acid [administration & dosage]; Calcium [administration & dosage]; Leg; Magnesium [administration & dosage]; Muscle Cramp [*therapy]; Pain Management [methods]; Pregnancy Complications [*therapy]; Randomized Controlled Trials as Topic; Vitamin B Complex [administration & dosage]; Vitamins [administration & dosage]

MeSH check words

Adult; Female; Humans; Pregnancy