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Supplementation with multiple micronutrients for breastfeeding women for improving outcomes for the mother and baby (Review)

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Supplementation with multiple micronutrients for breastfeeding women for improving outcomes for the mother and baby.
Cochrane Database of Systematic Reviews 2016, Issue 2. Art. No.: CD010647.
DOI: 10.1002/14651858.CD010647.pub2.

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[Intervention Review]

Supplementation with multiple micronutrients for breastfeeding women for improving outcomes for the mother and baby

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Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New, published in Issue 2, 2016.

Citation: Abe SK, Balogun OO, Ota E, Takahashi K, Mori R. Supplementation with multiple micronutrients for breastfeeding women for improving outcomes for the mother and baby. *Cochrane Database of Systematic Reviews* 2016, Issue 2. Art. No.: CD010647. DOI: 10.1002/14651858.CD010647.pub2.

ABSTRACT

Background

Globally, more than two billion people are estimated to be deficient in key vitamins and minerals, particularly iodine, iron and zinc. The majority of these people live in low-income settings and are typically deficient in more than one micronutrient. However, micronutrient deficiency among breastfeeding mothers and their infants also remains an issue in high-income settings, specifically among women who avoid meat and/or milk, women who may lack sufficient supplies of vitamin B12 and vitamin D, and/or women who are iron-deficient. Young children, pregnant and lactating women are particularly vulnerable to micronutrient deficiencies. They not only have a relatively greater need for vitamins and minerals because of their physiological state, but are also more susceptible to the harmful consequences of deficiencies. Multiple-micronutrient supplementation might be an option to solve these problems.

Objectives

The objective of this review was to evaluate the effects of multiple-micronutrient supplementation in breastfeeding mothers on maternal and infant outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2015) and reference lists of retrieved studies.

Selection criteria

Randomised controlled trials of multiple-micronutrient supplementation of three or more micronutrients versus placebo, no supplementation or supplementation with two or fewer micronutrients, irrespective of dosage of micronutrients, in breastfeeding mothers.

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 found no studies that compared multiple-micronutrient supplementation (with three or more micronutrients) versus supplementation with two or fewer micronutrients.

Two small studies (involving a total of 52 women) were included. One study compared multiple micronutrients with placebo and the other study compared multiple micronutrients with a group who received no supplementation. The studies were carried out in Brazil (36 adolescent mothers) and the USA (16 women) and included women with a low socioeconomic status. A lack of information in the study reports meant that risk of bias could not be adequately assessed (unclear risk of bias for many domains). There were no quantitative data for any of this review's outcomes so meta-analysis was not possible.

Neither of the studies reported on the primary outcomes of interest in this review: **maternal morbidity (febrile illness, respiratory tract infection, diarrhoea)**, **adverse effects of micronutrients within three days of receiving the supplement**, **infant mortality (defined as a child dying before completing the first year of age)**.

One study reported qualitatively on **maternal anaemia** (a secondary outcome of this review) - the study found that multiple-micronutrient supplementation was effective for recuperating from anaemia but there were no data for inclusion in our analyses. **Maternal satisfaction** was not reported in the included studies. Similarly, none of this review's infant secondary outcomes were reported in the included studies: **clinical micronutrient deficiency**; **morbidity episodes (febrile illness, respiratory tract infection, diarrhoea, other)**, **adverse effects of micronutrients within three days of receiving the supplement**.

Authors' conclusions

We found no evidence to quantitatively assess the effectiveness of multiple-micronutrient supplementation in improving health outcomes in mother and baby. The results of this review are limited by the small numbers of studies available, small sample sizes and the studies not reporting on the outcomes of interest in this review. There is no evidence to evaluate potential adverse effects of multiple-micronutrient supplements, particularly excess dosages.

There is a need for high-quality studies to assess the effectiveness and safety of multiple-micronutrient supplementation for breastfeeding women for improving outcomes for the mother and her baby. Further research should focus on whether multiple-micronutrient supplementation during lactation compared with none, a placebo or supplementation with fewer than two micronutrients is beneficial to maternal and infant health outcomes. Future studies should collect data on outcomes beyond micronutrient concentrations, for example: maternal and infant morbidity, adverse effects, maternal satisfaction, the risks of excess supplementation, and potential adverse interactions between the micronutrients and the other outcomes. This would help to bridge the gap between research on intermediary outcomes and health outcomes in order to develop sound policy in this field. Future studies could more precisely assess a variety of multiple-micronutrient combinations and different dosages and look at how these affect maternal and infant health outcomes. Larger studies with longer follow-up would improve the quality of studies and provide stronger evidence. In most of the included studies, bias could not be adequately assessed due to lack of information, therefore attention should be given to adequate methods of randomisation and allocation concealment, adequate methods of blinding of the participants, providers and the outcome assessors to improve the methodological quality of studies in this field.

PLAIN LANGUAGE SUMMARY

Multiple micronutrient supplementation for breastfeeding women for improving outcomes for the mother and her baby

The benefits and risks of multiple-micronutrient supplementation during lactation are not clear from randomised controlled studies. Key vitamins and minerals, particularly iodine, iron and zinc, are required in small amounts to ensure normal body metabolism, physical growth and development. Nutrient deficiency affects nearly one third of the world’s population, especially in low- and middle-income countries. Breastfeeding mothers need higher levels than usual in order to provide sufficient vitamins and minerals for their own health and that of their babies, particularly for normal functioning and the growth and development of the baby.

Previous studies have assessed supplementation of individual micronutrients. This review looked at the use of multiple-micronutrient supplements for breastfeeding women for improving outcomes for the mother and her baby. We searched for studies on 30 September 2015 and identified two small studies (involving 52 women) for inclusion in this review. The studies were carried out in Brazil and the USA and included women who had a low socioeconomic status. The studies were poorly reported and this lack of information made it difficult to determine whether the studies were at risk of bias. Neither of the studies provided data for any of this review's important outcomes: maternal illness (fever, respiratory infection, diarrhoea), adverse effects of micronutrients within three days of taking them, infant death (defined as a child dying before reaching one year of age).

Similarly, there were no data for any of the other outcomes that we were interested in. For the mother, these outcomes were maternal anaemia, and women's satisfaction. For the baby, these outcomes were micronutrient deficiency; illness episodes (fever, respiratory infection, diarrhoea, other), adverse effects of micronutrients within three days of the woman receiving the supplement. However, one of the included studies reported that multiple-micronutrient supplementation was effective for lactating women recuperating from anaemia.

There is a need for high-quality studies to assess the effectiveness and safety of multiple-micronutrient supplementation for breastfeeding women for improving outcomes for the mother and her baby. Larger studies with longer-term follow-up would improve the quality of studies and provide stronger evidence. Further research should focus on whether multiple-micronutrient supplementation during lactation (compared with no supplementation, a placebo or supplementation with fewer than two micronutrients) is beneficial to the mother and her baby and any associated adverse effects of the intervention. Futher studies should report on important outcomes such

as those listed in this review and consider the risks of excess supplementation. Future studies could more precisely assess a variety of multiple-micronutrient combinations and different dosages and look at how these effect outcomes for the mother and her baby.

BACKGROUND

Micronutrients are essential vitamins and minerals required in small amounts by the human body to ensure normal metabolism, physical growth and development, Occuring naturally, they are found in a variety of plant- and animal-based foods. While a varied diet typically provides all of the vitamins and minerals necessary for human health, in some settings, such foods are not available and provide a major threat to the health and development of populations. Therefore, due to poor quality of diet and/or inadequate intake of certain foods, micronutrient deficiency is highly prevalent, and constitutes a major global health problem. The World Health Organization (WHO) estimates that about 1.6 billion people are affected by anaemia worldwide (WHO 2008), or about one quarter of the population, the highest prevalence found in preschool age children; while the population group with the greatest number of individuals affected is non-pregnant women, which includes lactating mothers. Globally, the most significant contributor to the onset of anaemia is iron deficiency (Haidar 2010; WHO 2001). Thus, anaemia and iron-deficiency anaemia (IDA) are often used synonymously, and the prevalence of anaemia has often been used as a proxy for IDA. It is also estimated that 17.3% of the world's population is at risk of inadequate zinc intake (Wessells 2012). Vitamin A deficiency, affecting an estimated 190 million preschool age children (WHO 2009) significantly increases the risk of severe illness, and even death, from common childhood infections as diarrhoeal disease and measles, and is a leading cause of severe visual impairment. Moreover, these deficiency problems are known to overlap and interact leading to multiple-micronutrient deficiencies in most affected populations.

Although the majority of people deficient in key vitamins and minerals live in low-income settings (De Benoist 2008; Haidar 2010; Wessells 2012; WHO 2001; WHO 2008; WHO 2009), micronutrient deficiency is a public health problem affecting populations in both high- and low-income countries. Particularly, young children, pregnant and lactating women are especially vulnerable to micronutrient deficiencies. Vitamin and mineral deficiencies in pregnancy and lactation are associated with adverse health outcomes in both the mother and her breast-fed infant. They not only have a relatively greater need for vitamins and minerals because of their physiological state, but are also more susceptible to the harmful consequences of deficiencies (WHO 2006). Among breastfeeding women, the nutritive demands of lactation are considerably greater than those of pregnancy (IOM 1991). In the first four to six months after birth, infants double their birthweight and lactation is viewed as successful when the fully breast-fed infant is growing well and maintaining appropriate biochemical indexes of nutritional status (Picciano 2003). It is generally assumed that the nutritional demands of lactation are directly proportional to the intensity and duration of breastfeeding and at nutrient intakes less than recommended, maternal intakes of some micronutrients are correspondingly low (Jensen 1995).

Breast milk has been proven to be adequate as the sole source of nutrition up to age six months, providing that the maternal diet and reserves are adequate and a sufficient quantity is being transferred to the infant (Kramer 2004). However, measurable differences in milk nutrient content can and do occur due to dietary intake, especially in the vitamin constituents, particularly vitamin A and B (Picciano 2001). The nutritional requirements of the breastfeeding woman thus increase to support infant growth and development as well as maternal metabolism.

Description of the condition

The unmet requirements for most micronutrients in lactating women can result in various adverse effects for both mother and infant as the mother's micronutrient status determines the health and development of her breast-fed infant. Low maternal nutrient intake during lactation remains a problem in many parts of in the world, especially in low-income settings such as Sub-Saharan Africa (Lartey 2008). This results in major shortfalls in the concentration of some of these nutrients in breast milk, thus providing sub-optimal levels of nourishment to the nursing infant (Dijkhuizen 2001; McCullough 1990).

The WHO currently recommends iron and folic acid supplementation to reduce the risk of iron-deficiency anaemia among pregnant women. Available evidence further shows that giving multiple-micronutrient supplements to pregnant women could improve pregnancy and birth outcomes (Haider 2011; Haider 2015; Kawai 2011), Given that the nutritive demands of lactation are considerably greater than those of pregnancy (Picciano 2003) the use of multiple-micronutrient supplementation in breastfeeding mothers may be a promising strategy for improving the nutritional and health outcomes in infants through improved maternal nutritional and immune status (Allen 2005).

In relation to the level of importance to the mother-infant pair during lactation, micronutrients have been divided into two priority groups defined by maternal status or intake of each nutrient, its concentration in breast milk and the efficacy of supplementation (Allen 1994). Priority group one generally includes water-soluble vitamins: B vitamins - thiamin, riboflavin, vitamin B6 and B12 as well as vitamin A, and in endemically-deficient populations, iodine and selenium. Breast milk is the major source of these micronutrients for the infant and the amounts present in breast milk are highly variable depending on maternal intake. Priority group two includes folic acid, vitamin D, calcium, iron, copper and zinc. For this group, maternal status or dietary intake has relatively little effect on their concentration in human milk. Consequently, the suckling infant is comparatively well protected from maternal deficiency and the mother runs the greatest risk of depletion during lactation if her intake does not meet requirements (Allen 1994).

Description of the intervention

Lactation places high demands on maternal energy stores relative to other physiological stages in the life cycle, and likewise, the requirements for most micronutrients are also higher. The theoretical basis for such increased requirement is well documented (Delange 2004; Hollis 2004; IOM 2001; Picciano 2003), and lactating women who are not sufficiently nourished risk maternal depletion of micronutrient stores.

Vitamin A: Maternal deficiency in vitamin A prevents vitamin build-up of the infant's liver stores and consequently fails to offer protection from deficiency beyond six months of age. Given the benefit of maternal vitamin A status, supplementation of women with 200,000 international units (IU) of vitamin A postpartum is recommended in populations deficient in vitamin A (Ross 2002; WHO 1997). However, collective evidence from randomised controlled trials demonstrates only a modest

improvement in maternal serum and milk retinol following vitamin A supplementation in postpartum women (Oliveira-Menegozzo 2010). A Cochrane review that examined the impact of vitamin A supplementation in postpartum breastfeeding mothers in low- and middle-income countries on morbidity and mortality in infants less than six months old also found that there is insufficient evidence to show that either maternal postpartum or infant vitamin A supplementation results in a reduction in infant morbidity or mortality (Gogia 2011). In yet another Cochrane review investigating the effectiveness of vitamin A supplementation during pregnancy on maternal and newborn clinical outcomes, McCauley 2015 concluded that the effect of vitamin A supplementation would depend on whether the recipient population is deficient or not. In populations that are vitamin A deficient and in HIV-positive pregnant women, antenatal administration of vitamin A has resulted in reduction in maternal anaemia and infection (McCauley 2015). Previous systematic reviews (Gogia 2011; Oliveira-Menegozzo 2010; McCauley 2015) have addressed the effectiveness of vitamin A supplementation in improving maternal and child health outcomes, and it is thus excluded from the current review.

B vitamins: Generally, B complex vitamin deficiency is partially caused by lack of meat and dairy in the diet. Infants born to mothers whose B vitamin status is inadequate have been shown to be at high risk of developing a deficiency of these vitamins, as well as any consequences for infant health (Allen 2012).

Thiamine (vitamin B1) deficiency, otherwise known as beri-beri, and characterised by myocardial alterations with congestive heart failure, oedema and peripheral neuritis is still relatively common (Harper 2006). Maternal thiamine deficiency can rapidly result in depletion of the vitamin in breast milk, however, breast milk contents have been shown to be improved with supplementation (Allen 2012). Studies conducted among pregnant and lactating women in Thailand show that maternal supplementation improved vitamin concentrations in breast milk (McGready 2001; Stuetz 2012). In a study to assess thiamine status of lactating mothers from Maela refugee camp, the routine provision of daily 100 mg of thiamine mononitrate postpartum compared to the previous weekly 10 mg of thiamine hydrochloride resulted in significantly higher total thiamine in breast milk (Stuetz 2012). In a separate study among Thai Karen women, supplementation ensured adequate breast milk thiamine levels despite the presence of biochemical deficiency (McGready 2001).

Riboflavin (vitamin B2) concentrations in breast milk are also sensitive to maternal riboflavin intake. A study in rural Gambia measuring the riboflavin status in infants between birth and two years of age showed that infants born to riboflavin-deficient mothers were deficient at birth, and remained so throughout suckling and weaning in comparison to a supplemented group (Bates 1982a). Maternal supplementation with riboflavin also improved clinical signs associated with riboflavin deficiency in the supplemented group, reducing the mean activation coefficient (AC) of erythrocyte glutathione reductase from 1.62 to 1.19 within three weeks. Breast milk riboflavin levels were increased in supplemented women and their infants' AC's were reduced, compared with the placebo group (Bates 1982b).

Niacin (vitamin B3) deficiency typically results in pellagra, which is characterised by dementia, dermatitis and diarrhoea (Prakash 2008). Deficiency of vitamin B3 is often interrelated with riboflavin and vitamin B6 deficiencies (WHO 2005), thus multiple-micronutrient supplementation is important. The recommended additional dose for lactating women is 2.4 mg niacin equivalents (NE)/day - 1.4 mg of niacin are secreted daily and 1 mg is needed for lactation energy expenditure (WHO 2005). Therefore, the total recommended nutrient intake (RNI) for lactating women is 17 mg/day (WHO 2005).

Vitamin B6 deficiency usually occurs in combination with other B-complex vitamins (McCormick 1988), underscoring the need for multiple-micronutrient supplementation. Several studies assessing the effects of maternal supplementation on vitamin B6 concentrations of milk and the consequences of infant function showed that vitamin B6 intake in infants was correlated with levels of maternal supplementation (Chang 2002; Kang-Yoon 1992; McCullough 1990). Maternal vitamin B6 status was found to correlate strongly with infant behaviour among American (Chang 2002; Kang-Yoon 1992) and Egyptian mother-infant pairs (McCullough 1990). Findings from the Egyptian study further indicated that adequate maternal vitamin B6 status was associated with easier consolability and better irritability response of infants when adverse stimuli were presented (McCullough 1990).

Although dietary vitamin B12 deficiency in infancy is rare, a few cases have been reported, most of whom are breast-fed infants of mothers who themselves were deficient in the vitamin (Citak 2011; Emery 1997; Weiss 2004). Clinical manifestations of vitamin B12 deficiency include the development of haematological, neurological and metabolic abnormalities in breast-fed infants of mothers themselves deficient in the vitamin. In the case of a five-month old breast-fed infant, deficiency was due to low vitamin B12 concentrations in the maternal breast milk and treatment of the infant with vitamin B12 resulted in a rapid clinical and haematological improvement (McPhee 1988). Similar recovery was also observed in other reported cases of vitamin B12 deficiency resulting from inadequate maternal intake (Citak 2011; Weiss 2004). There is a dearth of research on the effect of oral supplementation in lactating women and the usual therapeutic response is to give a high (500 µg to 1000 µg) intramuscular dose of vitamin B12 to both mother and infant once presenting with clinical symptoms (Allen 2012). Nonetheless, oral supplementation of women throughout pregnancy and early in lactation might be effective in improving vitamin B12 status of mothers and infants who are nutritionally at risk of deficiency (Duggan 2014). The interaction of vitamin B12 with folate may also be important in the prevention of anaemia (WHO 2005).

Folic acid (folate) needs during lactation are increased due to the important role folate plays in DNA, RNA and protein biosynthesis (O'Connor 1997). Despite maternal intake not affecting concentrations in milk unless the maternal deficiency is severe, there may be consequences for the mother-infant pair which have not been sufficiently researched (O'Connor 1997). The RNI for lactating women is 500 µg/day (WHO 2005).

Vitamin C deficiency presents as scurvy (WHO 2005), and the WHO recommends an extra 25 mg of vitamin C for lactating women due to 20 mg daily secretion and an absorption efficiency of 85% (WHO 2005). Similar to other group I vitamins, maternal intake of vitamin C is known to influence the concentration of vitamin C in breast milk. In a study among Finnish mother-infant pairs to determine the nutritional adequacy of breastfeeding, the mother's intake of vitamin C influenced plasma and milk concentration of the vitamin

(Salmenpera 1984). Although plasma vitamin C concentration was improved by supplementation, exclusively breast-fed infants were able to maintain their plasma vitamin C concentration at the same or higher concentration than the vitamin C-supplemented controls (Salmenpera 1984). The total RNI to fulfil the needs of the mother-infant pair is 70 mg/day (WHO 2005).

Breast-fed infants are at high risk for vitamin D deficiency (Specker 1985). Unlike most group I vitamins, breast milk content of vitamin D is considered as not very responsive to increased maternal intakes (Picciano 2006). The WHO/FAO (Food and Agriculture Organization) joint report concluded that vitamin D supplementation is not necessary; however, it encourages good nutrition and sunshine exposure to mothers and infants (WHO 2005). Conversely, evidence from randomised controlled trials suggests the beneficial effect of maternal cholecalciferol supplementation on the vitamin D status of breast-fed infants (Hollis 2004; Oberhelman 2013). In the US, a single dose (150,000 IU) or daily dose (5000 IU/day) of cholecalciferol supplementation of mothers during lactation provided improved breast milk concentrations that resulted in sufficient vitamin D levels for breast-fed infant (Oberhelman 2013). In a separate study involving fully lactating women, high-dose (1600 or 3600 IU/day) vitamin D2 supplementation over a three-month period safely increased circulating 25-hydroxyvitamin D concentrations for both groups (Hollis 2004). According to the WHO recommendation, the RNI for lactating women is 5 µg/day (WHO 2005).

Generally, there are no specific recommendations for vitamin E supplementation in lactating women (SACN 2012). However, the Institute of Medicine's (IOM) recommended dietary allowance (RDA) is 19 mg/day for lactating women, up from 15 mg/day for non-lactating, non-pregnant women (SACN 2012).

Breast milk content of iron, copper and zinc with their physiological pattern of decline during lactation appears to be uninfluenced by maternal dietary intake making the mother especially vulnerable to depletion during lactation (Allen 1994). Observational studies have found no correlation between maternal mean dietary intake of zinc, copper, and iron with their concentrations in breast milk (Hannan 2009; Mahdavi 2010).

The copper content in milk is highest soon after birth and decreases over the course of lactation (IOM 2001; Yalcin 2015), and maternal copper status is relatively unaffected by plasma copper level (Domellöf 2004). Plasma copper levels were not correlated with milk copper concentration and complementary food energy intake in a multi-site study examining the associations between breast milk concentrations of iron, zinc, and copper and maternal mineral status (Domellöf 2004). However, there are no indications that the copper content of human milk is inadequate to maintain copper status in infants. According to a report compiled by the IOM Panel on Micronutrients in 2001, the mean copper content of human milk during the first six months of lactation is approximately 250 µg/L (IOM 2001). While the WHO/FAO have not set a RNI for copper, the IOM set the RDA at 1300 µg/day for lactating women, up 400 µg/day compared to non-lactating women (SACN 2012).

The selenium content of human milk has been shown to be sensitive to changes in maternal dietary selenium (Kumpulainen 1985). Selenium RNI for lactating women is calculated based on the selenium needed to meet requirements for lactation in infants aged nought to six months and seven to 12 months, respectively. According to the WHO, the total RNI for lactating women is 35 µg/day (nought to six months) and 42 µg/day (seven to 12 months) (WHO 2005).

Iodine concentration in breast milk varies by maternal dietary iodine intake, either supplemented or consumed in natural foods (Semba 2001), being lowest in areas of iodine deficiency and high prevalence of goitre. However, milk iodine levels are known to be correspondingly higher when programmes of iodine prophylaxis such as salt iodisation or administration of iodised oil are implemented (Azizi 2009). A systematic review that examined the effect of iodine deficiency in pregnancy and infancy concluded that in moderate to severe iodine-deficient areas, iodine supplementation before or during pregnancy eliminates new cases of cretinism while improving perinatal outcomes (Zimmermann 2012). However, the conclusions may differ from the effects of supplementation during lactation. A separate Cochrane review (Angermayr 2004) described the effects of iodine supplementation in the prevention of iodine deficiency disorders in children. Angermayr and colleagues suggested that iodine supplementation is an effective means of decreasing goitre rates and improving iodine status in children (Angermayr 2004). Based on evidence such as these, the WHO together with UNICEF recommend a daily dose of iodine supplement of 90 µg/day for children less than two years and 250 µg/day for lactating women (Andersson 2007).

Given the significant impact of deficiency in key micronutrients, women could potentially benefit from a supplement containing multiple vitamins and minerals (defined as containing at least three micronutrients). One potential benefit of multiple-micronutrient supplementation could be that they may be comparable to the iron-folate regimen in reducing anaemia. Evidence from randomised controlled trials on the effect of supplementation with multiple micronutrients versus iron and folic acid on pregnancy outcomes in developing countries show that the provision of multiple micronutrients is effective in improving neonatal and perinatal outcomes (Kawai 2011). Similarly, when compared with supplementation with two or less micronutrients or no supplementation or with placebo, multiple-micronutrient supplementation resulted in significantly decreased number of low birthweight babies (risk ratio (RR) 0.83; 95% confidence interval (CI) 0.76 to 0.91), small-for-gestational-age babies (RR 0.92; 95% CI 0.86 to 0.99) (Haider 2015). The beneficial effect of such supplementation on improving maternal and child outcomes postpartum is however limited. A large trial that examined the effect of maternal food and micronutrient supplementation during pregnancy to three months postpartum on infant micronutrient status found limited differential effects between maternal food or micronutrient supplementation groups (Eneroth 2010). The study however concluded that maternal multiple-micronutrient supplementation was associated with improved vitamin B12 status in infants (Eneroth 2010).

Acceptability and adherence rates to supplementation with multiple micronutrients have also been shown to be comparable to routine supplementation regimens (Adu-Afarwuah 2011; Aguayo 2005). A study assessing the acceptability of multiple micronutrients by pregnant and lactating women in Mali observed no differences between comparison groups with respect to women's perceptions about supplement size, colour, taste or flavour. Furthermore, better adherence was observed in the multiple micronutrient as compared to the iron and folic

acid supplementation scheme (Aguayo 2005). Another trial in Ghana investigating the acceptability of lipid-based multiple-micronutrient supplements formulated for infant and pregnant or lactating women found that supplements were well accepted among all groups (Adu-Afarwuah 2011).

How the intervention might work

Single nutrient interventions have been implemented across vulnerable populations in many parts of the world to prevent those micronutrient deficiencies of greatest public health importance, notably vitamin A and iron-folate combination (Angermayr 2004; Michelazzo 2013; Thorne-Lyman 2012). The varied results in different populations have led researchers to question the possibility of concurrent micronutrient deficiencies (Ahmed 2007; Dijkhuizen 2001; Jiang 2005). Therefore, there is an increased interest in evaluating the benefit of multiple-micronutrient supplements in breastfeeding women, because it is possible that deficiencies in one nutrient may be a marker for other nutrient inadequacies. For example, an observational study in Indonesia showed that the micronutrient status of lactating mothers and that of their infants were closely related with deficiencies of vitamin A, iron and zinc occurring concurrently in both mother and infant (Dijkhuizen 2001). Another study conducted among rural Nepali pregnant women revealed that multiple-micronutrient deficiencies were common among pregnant women (Jiang 2005). Over 10% of the participants were found to be anaemic and deficient in B-complex vitamins, and approximately 20% of the women had deficiencies of two or more vitamins, implying that inadequacy of a single nutrient was likely associated with deficiencies of other micronutrients (Jiang 2005). Prior research has shown that coexisting nutritional deficiencies can limit the potential benefit of a single nutrient supplement in improving nutrition status and morbidity (Fishman 2000; Suharno 1993). For instance, vitamin A (Suharno 1993), riboflavin, vitamin B6, vitamin B12 (Ahmed 2007; Allen 2000), and folate (Fishman 2000; Koury 2004) are suggested to exert a haematopoietic function. This suggests that anaemic women should possibly be supplemented not only with iron but with a combination of micronutrients implied in the prevention of anaemia.

In spite of the current state of knowledge, little is known about metabolic interactions of micronutrients. Some authors have also questioned the effectiveness of multiple-micronutrient supplementation in improving nutritional status due to possible interactions that can cause impaired absorption (Ramakrishnan 2004; Sandström 2001). The lack of benefit of multiple-micronutrient supplements to improve maternal iron status during pregnancy has been reported (Ramakrishnan 2004), while prenatal iron supplements were found to adversely influence zinc absorption among Peruvian pregnant women (O'Brien 2000). However, micronutrient supplementation programs are influenced by a multiplicity of factors such as physiological requirements of the target population and bioavailability, thus findings should be interpreted within the context of the exposed population.

Why it is important to do this review

The WHO recommends that infants be exclusively breast-fed for the first six months of life. This feeding strategy has the potential to reduce the risk of infections while benefiting infant health and survival as well as maternal health. Accompanying this recommendation is the emphasis on the importance of the nutritional status in lactating women (Kramer 2004). Lactation is a complex hormonally-controlled anabolic state involving the redistribution of nutrients to the mammary glands for transfer to the infant (Picciano 2003). Micronutrients have a special role during lactation for maternal and infant health outcomes (Hermoso 2011). For example, vitamin D is necessary for healthy bone growth and the prevention of rickets and vitamin B6 (pyridoxine) is important for normal brain development and functioning of the central nervous system in infants. Therefore, maintaining adequate levels of essential nutrients in breast milk in lactating mothers is important. Despite this significance, the global status on the prevalence of micronutrient deficiency for various vitamins in lactating women is scarce. Additionally, the extent to which low intakes of micronutrients affect the success of lactation, maternal and infant health has not been sufficiently examined except when a distinct nutritional deficiency is evident in the nursing infant, for example, vitamin B6 (McCullough 1990) and riboflavin (Bates 1982b). Some studies and programs with the aim of improving mother's and infant's health focus on multiple-micronutrient supplementation of breastfeeding women. However, there are no consistent practices or recommendations. A systematic review of the current evidence regarding multiple-micronutrient supplementation for practice and policy is warranted.

OBJECTIVES

To evaluate the effects of multiple-micronutrient supplementation in breastfeeding mothers on maternal and infant outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All prospective randomised controlled trials evaluating multiple-micronutrient supplementation of breastfeeding mothers including individually-randomised or cluster-randomised trials, and multi-armed trials. Quasi-randomised trials and cross-over trials were not eligible for inclusion.

Types of participants

Non-pregnant mothers who exclusively fed breast milk or practiced mixed feeding (breast milk and formula). HIV-positive women were excluded from the review.

Types of interventions

Studies of multiple-micronutrient supplements of three or more micronutrients compared with placebo, no supplementation or supplementation with two or fewer micronutrients, irrespective of dosage of micronutrients. Trials with fewer than three supplements in the intervention group were excluded regardless of their outcome. There were no limits on the duration of supplementation.

Types of outcome measures

Primary outcomes

Maternal

1. Morbidity (febrile illness, respiratory tract infection, diarrhoea)
2. Adverse effects of micronutrients within three days of receiving the supplement

Infant

1. Infant mortality (defined as a child dying before completing the first year of age)

Secondary outcomes

Maternal

1. Anaemia (maternal haemoglobin level < 12 g/dL or maternal serum ferritin < 15 µg/L)
2. Satisfaction

Infant

1. Clinical micronutrient deficiency
2. Morbidity episodes (febrile illness, respiratory tract infection, diarrhoea, other)
3. Adverse effects of micronutrients within three days of receiving the supplement

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 (30 September 2015).

For full search methods used to populate the PCG Trials Register including the detailed 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, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth Group in *The Cochrane Library* and select the '***Specialized Register***' section from the options on the left side of the screen.

Briefly, 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.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth Group review topic (or topics), and is then added to the Register. The Trials Search Co-ordinator searches the Register for each review using this topic number rather than keywords. This results in a more specific search set which has been fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).

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 we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third person.

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 a third person. We entered data into Review Manager software (RevMan 2014) and checked for accuracy.

When information regarding any of the above was unclear, we attempted 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 included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement 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:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- 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 studies at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- 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:

- 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:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- 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);
- 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:

- 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);
- 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);
- 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.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other 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). 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.

The two included trials did not provide any data that could be included in an analysis. In future updates, if more data are available for analysis, we will use the methods for analysis as outlined in Appendix 1.

RESULTS

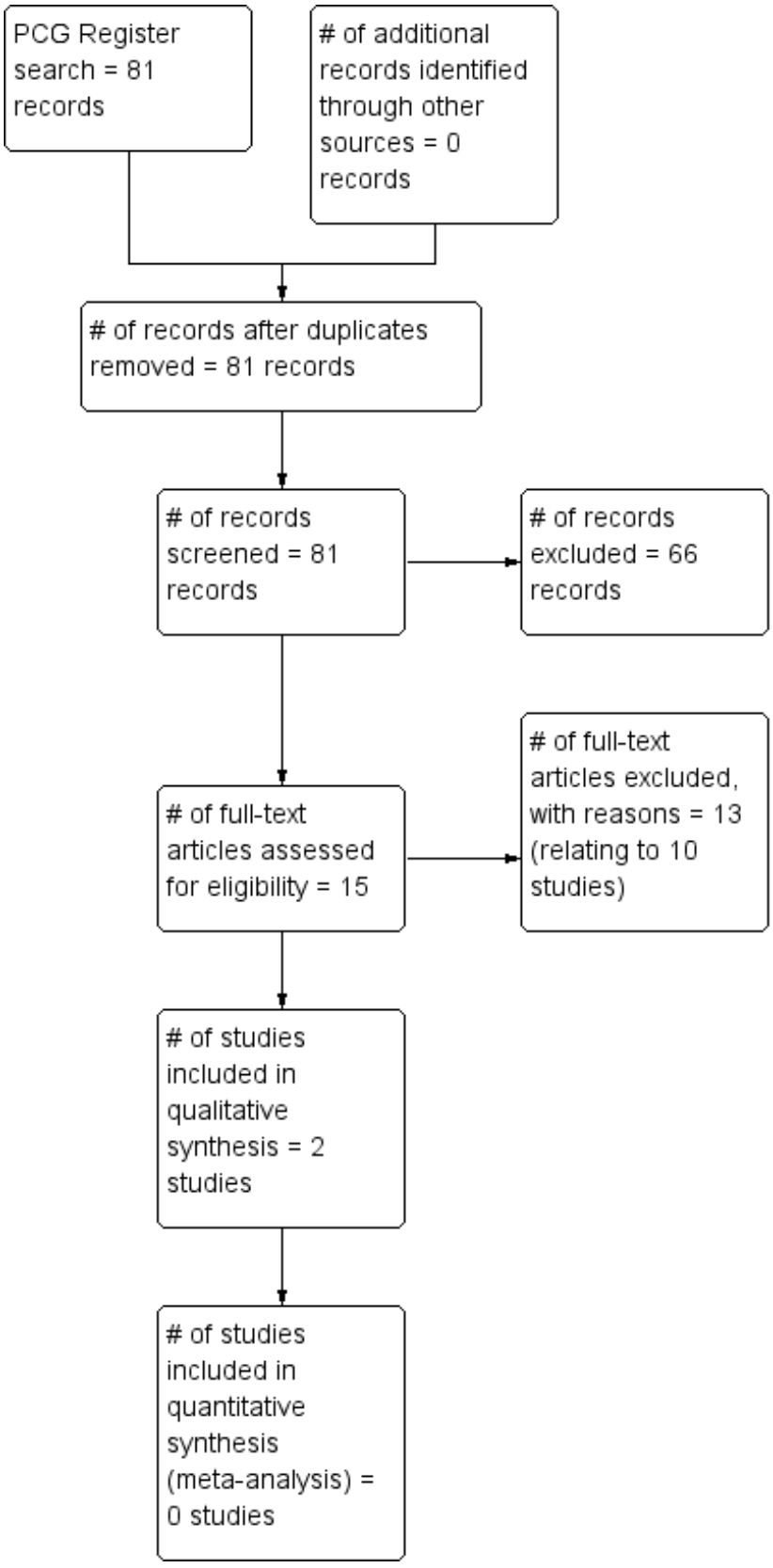
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Trials Register retrieved 81 trial reports but only two trials (Correia-Santos 2011; Sneed 1981) involving 52 women were eligible for inclusion in the current review. See Figure 1 for details.

Figure 1. Study flow diagram.



Included studies

Design

Correia-Santos 2011 utilised randomised block design (Correia-Santos 2011), while Sneed 1981 was a double-blind study (Sneed 1981).

Interventions

One of the studies (Correia-Santos 2011) assessed multiple-micronutrient supplementation versus placebo. Correia-Santos 2011 examined the impact of a nutritional supplement on the nutritional status of lactating adolescent mothers with low socioeconomic status. Participants were recruited from a hospital in Rio de Janeiro Brazil and the supplemented group received a multivitamin and multimineral supplement in addition to their traditional diet (n = 17), while those in the placebo group were maintained on a typical Brazilian diet without supplements (n = 19). In the Correia-Santos 2011 trial, the nutritional supplement provided 18 mg of Iron (ferrous fumarate), 15 mg of zinc (zinc oxide), 2 mg of copper (cupric oxide) and 162 mg of calcium (calcium phosphate dibasic), and other minerals and vitamins. Haemoglobin levels and plasma levels of iron, copper, zinc and calcium and were determined at seven (baseline), 11, and 15 weeks postpartum.

The second included study assessed daily multiple-micronutrient supplementation versus no supplementation in a population of lactating women in the USA (Sneed 1981). Milk samples were collected at five to seven days and 43 to 45 days postpartum, while fasting blood samples were drawn on the eighth and 46th days postpartum for analysis (Sneed 1981). The multivitamin-multimineral supplement in Sneed 1981 was composed of vitamin A 8000 IU, vitamin D 400 IU, vitamin E 30 IU, vitamin C 90 mg, folic acid 0.8 mg, thiamin 1.7 mg, riboflavin 2 mg, niacin 20 mg, vitamin B6 4 mg, vitamin B12 8 µg, calcium 200 mg, iodine 150 µg, iron 45 mg, magnesium 100 mg.

Participants

The two included trials involved 52 lactating women with low socioeconomic status. Correia-Santos 2011 involved 36 adolescent mothers who were non-vegetarian, had normal weight gain during pregnancy with uncomplicated pregnancies and delivery. All 36 participants in the study by Correia-Santos 2011 intended to breastfeed exclusively for at least 16 weeks. Physicians or health officials of the Women, Infant and Children (WIC) program recommended women participate in the second trial (Sneed 1981).

The 16 participants included eight primiparas and eight multiparas. In both studies, lactating mothers were divided into two groups.

Correia-Santos 2011: 36 adolescent lactating mothers: 17 received multiple-micronutrient supplements (mean age 16.3 years) versus 19 who received placebos (mean age 17.1 years).

Sneed 1981: 16 lactating women: nine supplemented versus seven unsupplemented.

Support or sponsorship

One included study did not state a funding or sponsorship source (Correia-Santos 2011). The second study received support from the Organized Research Grants of the Texas Woman's University, Denton, Texas, 76204 (Sneed 1981).

Baseline characteristics of participants

In both included studies, participants in the supplemented and placebo (unsupplemented) groups were from low socioeconomic status (Correia-Santos 2011; Sneed 1981). In one trial, the two groups of lactating adolescents were similar in all biochemical parameters measured at baseline with the exception of plasma copper (Correia-Santos 2011). Sneed 1981 did not describe the participant characteristics at baseline.

Studied outcomes

Neither of the included studies directly investigated relevant outcomes of interest. One study compared haemoglobin and haematocrit levels as well as plasma mineral content in the supplemented and placebo groups (Correia-Santos 2011). Sneed 1981 reported maternal micronutrients status and vitamin contents.

Excluded studies

Ten studies (13 reports) were excluded (Chierici 1999; Gonzalez-Cossio 1998; Khambalia 2006; Koppe 1955; Paoletti 2013; People's 1942; Salmenpera 1986; Shaaban 2005; SUMMIT 2008; Von Jaisle 1958). The SUMMIT 2008 trial included four publications of potential interest: Prado 2012a; Prado 2012b; Shankar 2008; Shankar 2009.

Risk of bias in included studies

The risk of bias was unclear overall due to lack of information in both study reports. See Figure 2; Figure 3 for a summary of 'Risk of bias' assessments.

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

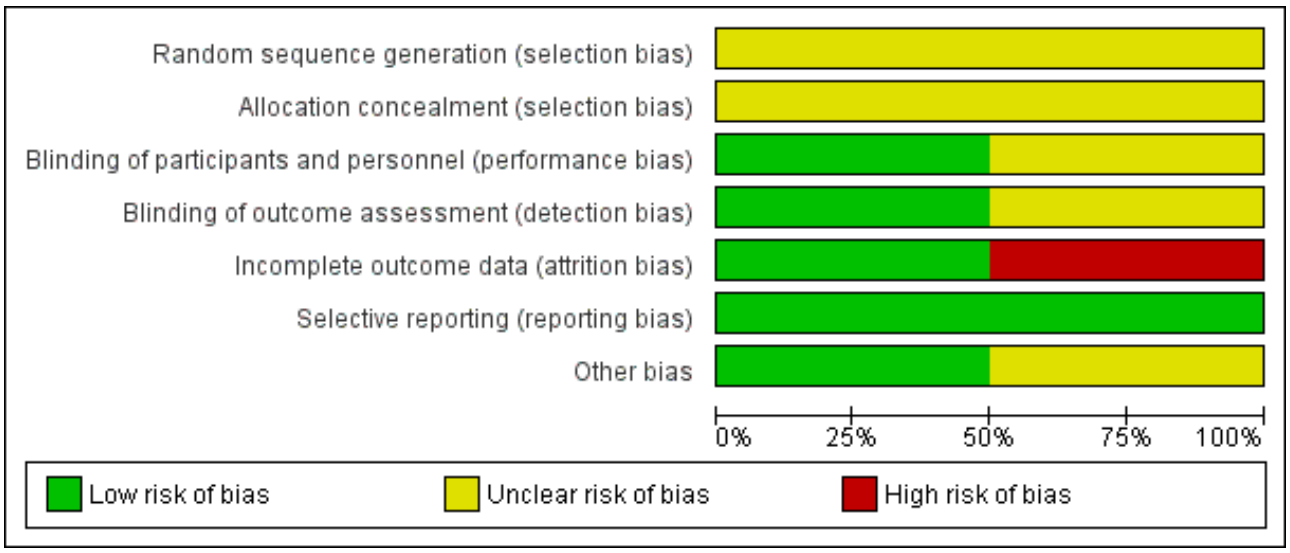
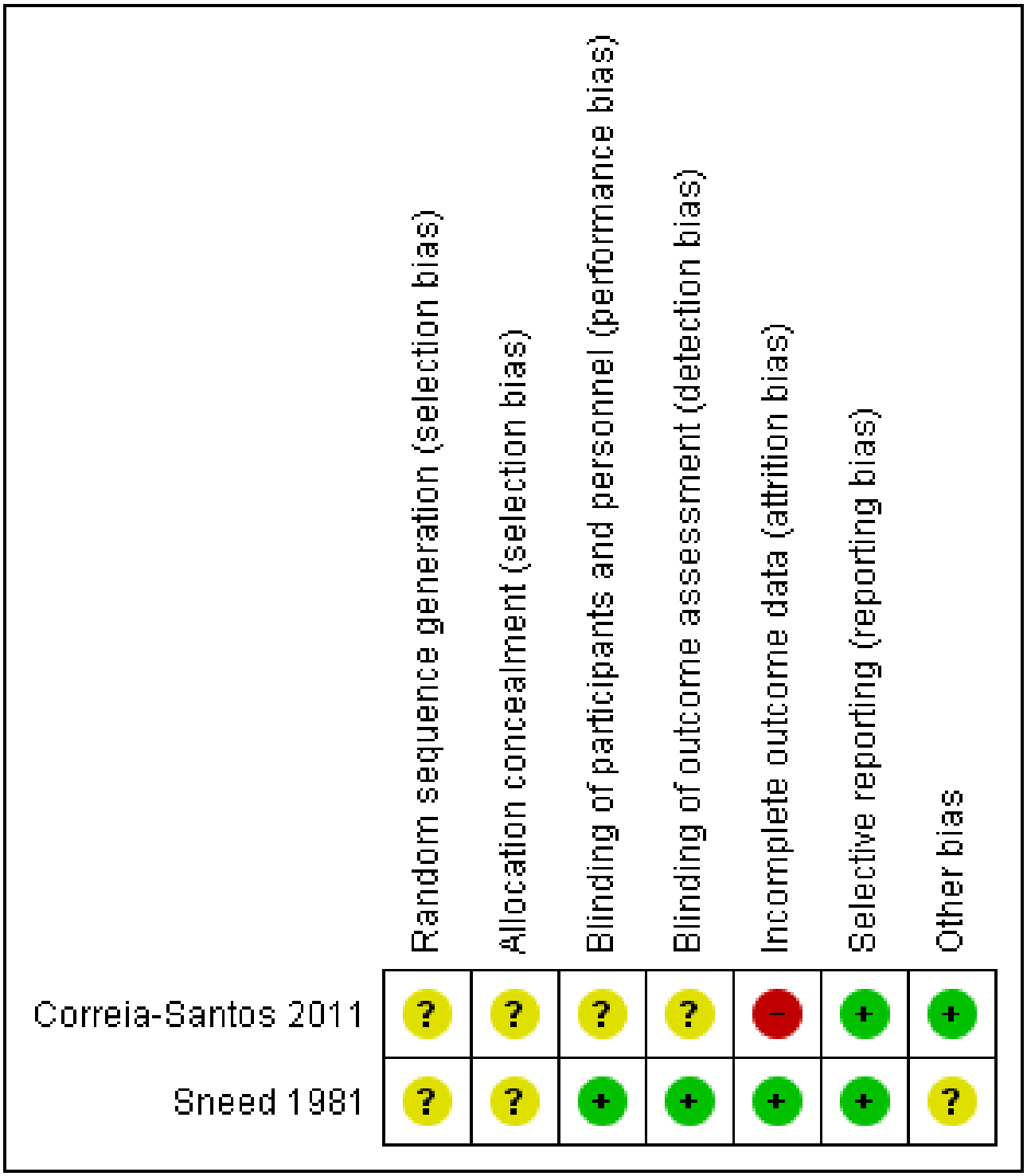


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Both studies were assessed as having an 'unclear' risk of bias for sequence generation and allocation concealment. In one of the studies (Correia-Santos 2011), randomisation of participants into groups was achieved using a randomised block design. However, it is unclear whether the process was by random sequence generation. In the second included trial (Sneed 1981), the method used for generating the randomisation sequence was not described. Neither of the studies clearly described allocation concealment, this may also be due to the year of publication of one of the included studies (Sneed 1981), which was before strict reporting guidelines were introduced.

Blinding

Although Sneed 1981 was reported as being a double-blind study (low risk of bias), it was not clear as to who was blinded. Further, multivitamin supplementation was allowed at the physicians discretion, while details regarding outcome assessors were not described (Sneed 1981). Blinding was not stated in the study by Correia-Santos 2011 (unclear risk of bias).

Incomplete outcome data

Sneed 1981 had no missing outcome data (low risk of bias), while Correia-Santos 2011 was assessed as potentially having a high risk of attrition bias. In the Correia-Santos 2011 study, participants who intended to breastfeed exclusively for at least 16 weeks were followed up providing three separate outcome measurements reported at seven, 11 and 15 weeks postpartum. In spite of the decreasing participant numbers, no explanation was reported regarding loss to follow-up.

Selective reporting

In both included studies pre-specified outcomes were reported (low risk of bias).

Other potential sources of bias

Correia-Santos 2011 was considered to be at a low risk of having other sources of bias. In contrast, the Sneed 1981 study was assessed as having an unclear risk of bias - the reporting of methods for this study was vague. In addition to groups being divided into supplemented and not supplemented, mineral supplementation was at the "physician's discretion". The trial report does not clearly state whether this applied to both groups and what type and dosage physicians actually recommended. Given that mineral supplementation is a component of the intervention, this could potentially influence the results.

Effects of interventions

Primary outcome measures

Neither of the included studies reported data relating to any of this review's primary outcomes.

Maternal

1. Morbidity (febrile illness, respiratory tract infection, diarrhoea)
2. Adverse effects of micronutrients within three days of receiving the supplement

Infant

1. Infant mortality (defined as a child dying before completing the first year of age)

Secondary outcome measures

Maternal

Anaemia (maternal haemoglobin level < 12 g/dL or maternal serum ferritin < 15 µg/L)

Only one study examined one of the secondary outcomes relevant to this review, maternal anaemia (Correia-Santos 2011). Multiple-micronutrient supplementation when compared with a placebo was effective for decreasing maternal anaemia at 11 weeks postpartum. Unlike the supplemented participants, 20% of participants in the placebo group were anaemic and showed mean haemoglobin concentrations below the normal value (12 g/dL), and significantly lower than the supplemented group (P = 0.0018) (Correia-Santos 2011). However, the mean haematocrit values were within the normal range for both groups. Evaluation of both parameters at 15 weeks postpartum showed that mean haemoglobin and haematocrit were comparable in both groups (Correia-Santos 2011).

Satisfaction

This outcome was not reported in the two included studies.

Infant

None of the infant secondary outcomes were reported in the two included studies. These outcomes were **clinical micronutrient deficiency**, **morbidity episodes (febrile illness, respiratory tract infection, diarrhoea, other)**, **adverse effects of micronutrients within three days of receiving the supplement**.

Other outcome measures

While the included studies did not allow us to evaluate this review's outcomes, some of the studies' qualitative key findings are worth noting. Correia-Santos 2011 also investigated the effect of multiple-micronutrient supplementation on haematocrit (expressed as packed cell volume (PCV)) and plasma mineral content. However, the latter were non significant aside from zinc. Sneed 1981 found that both groups of women in the study had similar milk ascorbic acid concentrations over the study period. Compared to the unsupplemented group, both the maternal vitamin B6 status and milk concentration of the vitamin increased in the supplemented group peaking at four to eight hours following supplementation. Breast milk concentrations of vitamin B12 and folic acid were significantly lower (P < 0.01) in the unsupplemented group of women at one and six weeks postpartum compared with the supplemented group. Conversely, no significant differences were reported in serum vitamin B12 and folic acid concentrations over the study period.

Adverse effects

One study found a negative association between multiple-micronutrient supplementation and plasma calcium but noted that this was due to interactions among the nutrients (Correia-Santos 2011).

DISCUSSION

This review aimed to address the important clinical question of multiple-micronutrient supplementation of three or more micronutrients compared with placebo, no supplementation or supplementation with two or less micronutrients irrespective of dosage in breastfeeding women in order to improve outcomes for the mother and her baby. The topic of multiple-micronutrient supplementation during lactation is critical due to its potential effects on the mother and baby, particularly women who are nutrient deficient in low-income settings. To date, relatively few studies have been published on the extent to which the nutrient content of breast milk is affected by maternal status and intake, and how this in turn affects maternal and infant health outcomes. Only two small studies (Correia-Santos 2011; Sneed 1981) were included in the current review limiting our assessment to a narrative description of the findings from the included studies. Multiple-

micronutrient supplementation among breastfeeding women was found to improve maternal nutritional status and breast milk content of various nutrients. However, both trials included in this review failed to examine the impact on maternal and infant health outcomes.

Similar to the Cochrane review on multiple-micronutrient supplementation during pregnancy (Haider 2015), potential adverse interactions and excess micronutrient supplementation could not be assessed as a result of the non-availability of data from studies included in this review. Only a limited amount of qualitative evidence could be included as the outcome data presented in both trials were not considered in the current review. These outcomes are easier to measure and quantify compared to other maternal and infant health outcomes such as adverse effects, morbidity or maternal satisfaction, which could include a wide range of measures and tools. However, such health outcomes which were the focus of investigation in this review are also important for formulating policy and guidelines on when and how maternal supplementation should occur.

While no concrete conclusions can be drawn regarding the effectiveness of multiple-micronutrient supplementation in comparison with single/double supplement or no supplement during lactation on the health outcomes of mothers and infants, the two included studies provide important contributions to the literature. It could be argued that randomised controlled trials are not always the most appropriate study design for this type of question because multiple-micronutrient supplementation is often encouraged especially in populations experiencing deficiencies. Including other study designs, such as observational studies, may provide additional evidence on relevant outcomes. Analysis comparing mothers supplementing and those not supplementing in a cohort for example would be possible. Those results may also be more generalisable. The logistics of conducting any study during this sensitive time of lactation may pose difficulties of its own. This is not to ignore the simple fact that conducting randomised controlled trials for multiple-micronutrient supplementation in breastfeeding women is an overlooked topic. The postpartum lactation period in general has received little attention from researchers in the past.

Summary of main results

Two studies involving 52 women were included in this review. Neither of the included studies provided data on any of our outcomes that could be included in an analysis. One trial reported that multiple-micronutrient supplementation showed full recuperation from anaemia in 36 breastfeeding adolescent mothers (Correia-Santos 2011).

Overall completeness and applicability of evidence

The included studies provide insufficient information to address the objectives of the review. However, the studies have provided some evidence regarding the intervention of multiple-micronutrient supplementation and benefits to the mother and baby. In one study, supplementation was beneficial for haemoglobin, copper and zinc levels among mothers (Correia-Santos 2011). The other study highlighted the importance of maintaining adequate levels of folic acid and vitamin B6 either through dietary intake or supplements (Sneed 1981).

Quality of the evidence

The two included studies were poorly reported, limiting our assessment of risk of bias, with many 'Risk of bias' domains assessed as 'unclear' risk of bias due to lack of information.

We were unable to assess the quality of the evidence using the GRADE approach because the included studies provided no quantitative data for any of this review's outcomes.

Potential biases in the review process

The strength of this review is the comprehensive search of the literature on multiple-micronutrient supplementation for breastfeeding women, with no language restrictions. A possible limitation of the review may be that one of the two included studies (Sneed 1981), predates 1990, when guidelines on how to report trials were not available. Since that time, many changes have been implemented in order to improve the quality of data reporting. This review is restricted to evidence from randomised controlled trials - it is possible that other study designs, such as non-randomised controlled studies, could also have provided evidence. Multi-micronutrient supplementation is widely encouraged and so observational studies, such as cohort studies, might have provided valuable data as well as grey literature.

Agreements and disagreements with other studies or reviews

This review is in agreement with the conclusions of a recent overview on the topic of multiple-micronutrient supplementation during pregnancy and lactation. This overview concludes that data on optimal dosage of supplementation during this period are lacking and that possible benefits of continued supplementation during lactation is mostly overlooked (Allen 2005).

AUTHORS' CONCLUSIONS

Implications for practice

The evidence provided in this review is insufficient to guide policy. Results are limited by a small number of studies, small sample sizes and the non-applicability of outcomes. The evidence on adverse effects is also insufficient to determine whether an excess dosage of multiple-micronutrient supplementation during lactation is harmful to the mother or her baby.

Implications for research

Further research is needed to determine whether multiple-micronutrient supplementation during lactation compared with none, a placebo or supplementation with fewer than two micronutrients is beneficial to maternal and infant health outcomes. Future studies should collect data on outcomes beyond micronutrient concentrations, for example: maternal and infant morbidity, adverse effects, maternal satisfaction, the risks of excess supplementation, and potential adverse interactions between the micronutrients and the other outcomes. This would help to bridge the gap between research on intermediary outcomes and health outcomes in order to develop sound policy in this field. Future studies could more precisely assess a variety of multiple-micronutrient combinations and different dosages and look at how these effect maternal and infant health outcomes. Larger studies with longer follow-up would improve the quality of studies and provide stronger evidence. In the two included studies, bias could

not be adequately assessed due to lack of information, therefore attention should be given to adequate methods of randomisation and allocation concealment, adequate methods of blinding of the participants, providers and the outcome assessors to improve the methodological quality of studies in this field.

ACKNOWLEDGEMENTS

As part of the pre-publication editorial process, this review has been 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.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Correia-Santos 2011

Methods	Randomised, placebo-controlled trial with block design.
Participants	36 lactating adolescent mothers (with a low socioeconomic status) were recruited from the maternity section of a hospital in Rio de Janeiro, Brazil. The women were non-vegetarian, had normal weight gain during pregnancy with uncomplicated pregnancies and delivery. All of the women intended to breast-feed exclusively for at least 16 weeks.

Correia-Santos 2011 *(Continued)*

Interventions	Intervention: daily multivitamin and multimineral supplementation which provided 18 mg of iron (ferrous fumarate), 15 mg of zinc (zinc oxide), 2 mg of copper (cupric oxide) and 162 mg of calcium (calcium phosphate dibasic) and other minerals and vitamins (p.393)). Control: placebo. The supplemented group received a multivitamin and multimineral supplement in addition to their traditional diet (n = 17) while the placebo group were maintained on a typical Brazilian diet without supplements (n = 19). The 2 groups of lactating adolescents were similar in all biochemical parameters measured at baseline with the exception of plasma copper.
Outcomes	Haematocrit (PCV), haemoglobin concentrations, plasma mineral content.
Notes	Haemoglobin level and plasma levels of iron, copper, zinc and calcium and were determined at 7 (baseline), 11 and 15 weeks postpartum. The trial report did not state any sources of funding or sponsorship.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sample randomisation in blocks.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment is unclear.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel is unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment is unclear.
Incomplete outcome data (attrition bias) All outcomes	High risk	The objective of the study was to follow women who intended to breastfeed exclusively for at least 16 weeks however, 3 separate measurements were reported 7, 11 and 15 weeks postpartum with decreasing participants, but no explanation is provided by the authors.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes are reported.
Other bias	Low risk	No other sources of bias were identified.

Sneed 1981

Methods	Double-blind study.
Participants	16 lactating women in the USA. Participants were recommended by physicians or health officials of the Women, Infant and Children (WIC) program. The 16 participants included 8 primiparas and 8 multiparas.

Sneed 1981 *(Continued)*

Interventions	Intervention (n = 9): daily multivitamin and multimineral supplementation (Natalins, a multivitamin and multimineral supplement: 8000 IU vitamin A, 400 IU vitamin D, 30 IU vitamin E, 90 mg vitamin C, 0.8 mg folic acid, 1.7 mg thiamin, 2 mg riboflavin, 20 mg niacin, 4 mg vitamin B6, 8 µg vitamin B12, 200 mg calcium, 150 µg iodine, 45 mg iron, and 100 mg magnesium (p.1339)). Control (n = 7): no supplementation.
Outcomes	Maternal micronutritional status and vitamin contents of breast milk. Milk samples were collected at five to seven days and 43 to 45 days postpartum: while fasting blood samples were drawn on the 8th and 46th days postpartum for analysis.
Notes	Composite multivitamin including vitamin A. The study received support from the Organized Research Grants of the Texas Woman's University, Denton, Texas, 76204. Participant characteristics at baseline were not described.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"divided into two lactation groups."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment is unclear.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were unaware of allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This is a double-blind study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes are reported.
Other bias	Unclear risk	Reporting of methods was rather vague. In addition to groups being divided into supplemented and not supplemented, mineral supplementation was at the "physician's discretion" p1339. The trial report does not clearly define whether this applied to both groups and what type and dosage physicians actually recommended. Given that mineral supplementation is a component of the intervention this could potentially influenced the results.

IU: international units
PCV: packed cell volume

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

Study	Reason for exclusion
Chierici 1999	Not an RCT.
Gonzalez-Cossio 1998	Intervention provided is a food supplement; control group received similar food supplement with lower energy content.
Khambalia 2006	Intervention and control are both multiple micronutrients, the control group did not receive iron.
Koppe 1955	Trial is not multiple-micronutrient study.
Paoletti 2013	The population were not breastfeeding women.
People's 1942	The population were not breastfeeding women.
Salmenpera 1986	Intervention and control are multiple micronutrients, the control group did not receive copper and zinc.
Shaaban 2005	Both groups received multiple-micronutrient supplementation 1 with and 1 without zinc.
SUMMIT 2008	The population included both pregnant and lactating women (and data were not reported separately).
Von Jaisle 1958	Not an RCT.

RCT: randomised controlled trial

APPENDICES

Appendix 1. Methods of analysis to be used in future updates of this review

Assessment of the quality of the evidence using GRADE

We will assess the overall quality of the evidence using the GRADE approach as outlined in the GRADE handbook for the main comparison: administration of a progestogen by any route for the prevention of preterm birth compared with placebo or no treatment. The quality of the evidence will be assessed for the following outcomes.

1. Maternal morbidity (febrile illness, respiratory tract infection, diarrhoea)
2. Maternal adverse effects of micronutrients within three days of receiving the supplement
3. Infant mortality (defined as a child dying before completing the first year of age)
4. Maternal anaemia (maternal haemoglobin level < 12 g/dL or maternal serum ferritin < 15 µg/L)
5. Infant clinical micronutrient deficiency
6. Infant morbidity episodes (febrile illness, respiratory tract infection, diarrhoea, other)
7. Infant adverse effects of micronutrients within three days of receiving the supplement

We will use the GRADEpro Guideline Development Tool 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 each of the above outcomes will be produced using GRADE methodology. 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 will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their standard errors using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Multi-armed trials

We will include multi-armed trials in the analyses. For studies that meet the review's inclusion criteria, we will analyse the relevant intervention groups using a pair-wise comparison of intervention groups. Groups will be combined into single pair-wise comparisons using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either the T^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

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 will carry out statistical analysis using the Review Manager software (RevMan 2014). 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 Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We will not undertake pre-specified subgroup analysis if there is no heterogeneity among the trials and the fixed-effect model will be used to pool the results. 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 carry out the following subgroup analyses of primary outcomes, if required and if sufficient data are available:

1. dosage of the micronutrients in the supplement;
2. type of supplement;
3. duration of supplementation;
4. type of control group (supplementation versus placebo/no supplement, or higher versus lower supplementation dose).

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

Sensitivity analysis

If we identify substantial heterogeneity, we will investigate it using sensitivity analyses. We will carry out sensitivity analysis to investigate the effect of trial quality for the risk of bias items.

CONTRIBUTIONS OF AUTHORS

Rintaro Mori (RM) is guarantor for the review. Sarah K Abe (SKA) and Olukunmi O Balogun (OOB) wrote the draft protocol with input from Erika Ota (EO) and RM. SKA and OOB screened the articles and completed data extraction for relevant papers. SKA drafted the review. OOB, EO, RM and Kenzo Takahashi (KT) provided critical revisions on intellectual content.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- National Center for Child Health and Development, Japan.

External sources

- Ministry of Health, Labour and Welfare, Japan.

  Health Labour Sciences Research Grant (No.13800128)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are some differences between our published protocol (Abe 2013) and the full review.

We have changed the title from 'Supplementation with multimicronutrients (excluding vitamin A) for breastfeeding women for improving outcomes for the mother and baby'.

Methods for dealing with multi-armed trials was not considered at the time of protocol development, but has now been added to the methods for use in future updates of this review.

We have added methods for the use of GRADE to determine the quality of the body of evidence - however, we have not used GRADE (or included a 'Summary of findings' table) in this version of the review due to insufficient data (there are no numeric data for any of our outcomes). We will use GRADE and prepare a 'Summary of findings' table in future updates of this review if more data become available.

Methods/types of outcomes/infant primary outcomes - we have removed the outcome 'child mortality' and edited the outcome 'infant mortality' to 'infant mortality (defined as a child dying before completing the first year of age).

Methods/types of outcomes/maternal secondary outcomes - we have added a definition for the outcome 'anaemia' (maternal haemoglobin level < 12 g/dL or maternal serum ferritin < 15 µg/L).

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Anemia [therapy]; Breast Feeding; Lactation; Micronutrients [*administration & dosage]; Mothers; Parity

MeSH check words

Adolescent; Female; Humans; Infant; Pregnancy