Multiple-micronutrient supplementation for women during pregnancy (Review)

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ABSTRACT

Background
Multiple-micronutrient deficiencies often coexist in low- to middle-income countries. They are exacerbated in pregnancy due to the increased demands, leading to potentially adverse effects on the mother. Substantive evidence regarding the effectiveness of multiple-micronutrient supplements (MMS) during pregnancy is not available.

Objectives
To evaluate the benefits to mother and infant of multiple-micronutrient supplements in pregnancy and assess the risk of excess supplementation and potential adverse interactions between micronutrients.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 December 2005).

Selection criteria
All prospective randomised controlled trials evaluating micronutrient supplementation during pregnancy and its effects on the pregnancy outcome.

Data collection and analysis
Two review authors independently assessed trial quality and extracted the data.

Main results
Nine trials (15,378 women) are included. When compared with supplementation of two or less micronutrients or no supplementation or a placebo, multiple-micronutrient supplementation resulted in a statistically significant decrease in the number of low birthweight babies (relative risk (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) and in maternal anaemia (RR 0.61; CI 0.52 to 0.71). However, these differences lost statistical significance when multiple-micronutrient supplementation was compared with iron folic acid supplementation alone. No statistically significant differences were shown for the outcomes of preterm births and perinatal mortality in any of the comparisons.

A number of prespecified clinically important outcomes could not be assessed due to insufficient or non-available data from the included trials. These include placental abruption, congenital anomalies including neural tube defects, premature rupture of membranes, pre-eclampsia, miscarriage, maternal mortality, neurodevelopmental delay, very preterm births, cost of supplementation, side-effects of supplements, maternal wellbeing or satisfaction and nutritional status of children.

Authors' conclusions
The evidence provided in this review is insufficient to suggest replacement of iron and folate supplementation with a multiple-micronutrient supplement. A reduction in the number of low birthweight and small-for-gestational-age babies and maternal anaemia has been found with a multiple-micronutrient supplement against supplementation with two or less micronutrients or none or a placebo, but analyses revealed no added benefit of multiple-micronutrient supplements compared with iron folic acid supplementation.

These results are limited by the small number of studies available. There is also insufficient evidence to identify adverse effects and to say that excess multiple-micronutrient supplementation during pregnancy is harmful to the mother or the fetus.

Further research is needed to find out the beneficial maternal or fetal effects and to assess the risk of excess supplementation and potential adverse interactions between the micronutrients.

PLAIN LANGUAGE SUMMARY

Not enough evidence on benefits and risks, especially with excess doses, of multi-micronutrient supplements in pregnancy

In low and middle-income countries, many women have poor diets and are deficient in nutrients and micronutrients which are required for good health. Micronutrients are vitamins and minerals that are only needed in very small quantities by the body but are important for normal functioning, growth and development. In pregnancy, with the need to provide nutrition for the baby too, these mothers often become even more deficient and this can impact, not only on their heath, but that of their babies too. The benefits of individual supplementation have been assessed elsewhere, but in this review the use of multi-micronutrient supplements was addressed. The review identified nine trials involving 15,378 women; all trials were undertaken in low or middle-income countries. There was a reduction in low birthweight and small-for-gestational-age babies and anaemia in mothers but these effects were lost when multi-micronutrient supplements were compared with iron folic acid supplements. However, more evidence of effect is needed. This is particularly so for any adverse effects, especially if excess doses are used.

BACKGROUND

Micronutrient deficiency around the world

Micronutrients are vitamins and minerals required in minute amounts for normal functioning, growth and development. Women in low-income countries often consume inadequate levels of micronutrients due to limited intake of animal products, fruits, vegetables, and fortified foods (Huffman 1998). The resulting micronutrient deficiencies are exacerbated in pregnancy, leading to potentially adverse effects on the mother such as anaemia, hypertension, complications of labour and even death (Ramakrishnan 1999). At least 50 million pregnant women in low-income countries are anaemic, primarily due to iron deficiency (Stoltzfus 1995). Vitamin A deficiency affects millions of women and children worldwide. A study carried out in Nepal, showed that 20% of pregnant and 27% of postpartum women were vitamin A deficient (West 1997). Approximately 100 million women of reproductive age suffer from iodine deficiency (Leslie 1991). An estimated 82% of pregnant women worldwide have inadequate intakes of zinc to meet the normative needs of pregnancy (Caulfield 1998). Suboptimal vitamin B6 status has been observed in Egypt among more than one-third of breastfeeding women, based on low breastmilk concentrations (Kirksey 1994). Low serum vitamin B12 has been observed among pregnant and lactating women in Mexico and low breastmilk B12 was reported in Kenya (Allen 1993).

Importance of micronutrients

Micronutrient status may play an important role in pregnancy and birth outcomes.

Iron deficiency results in anaemia, which may increase the risk of death from haemorrhage after delivery although its effects on fetal development and birth outcomes are still unclear.

Folic acid deficiency can lead to haematological consequences, pregnancy complications and congenital malformations but, again, the association with other birth outcomes is equivocal (Black 2001). A clinical trial by Botto et al has demonstrated a protective effect of multivitamin supplements and folic acid against neural tube defects and other defects, such as orofacial clefts and some heart defects, although the evidence is not as consistent or as strong as with neural tube defects (Botto 2002). This was further investigated by Lumley et al and periconceptional folate supplementation was found to have a strong protective effect against neural tube defects (Lumley 2001).

Severe iodine deficiency results in pregnancy loss, mental retardation and cretinism (Dunn 1993), but little is known for other outcomes especially in marginal iodine deficiency (Ramakrishnan 1999).

Deficiencies of other minerals such as magnesium, selenium, copper, and calcium have also been associated with complications of pregnancy, childbirth or fetal development (Black 2001). Magnesium deficiency especially has been linked with pre-eclampsia and preterm delivery (Chein 1996).

Vitamin A deficiency in pregnancy is known to result in night blindness, to increase the risk of maternal mortality and is associated with premature birth, intrauterine growth retardation, low birthweight and abruptio placentae (Ladipo 2000). A study from Nepal (West 1999) showed that weekly vitamin A supplementation reduced maternal mortality by 40%. West et al in 1997 (West

1997) showed that maternal mortality in Nepal decreased by about half in women who received vitamin A for at least three months before and during pregnancy (UNICEF 1998; West 1997). It was also found that the prevalence of iron-deficiency anaemia in pregnancy was reduced from 76% in controls to 69% among those receiving vitamin A (Stoltzfus 1997).

Zinc deficiency has been associated in some, but not all, studies with complications of pregnancy and delivery such as pre-eclampsia and premature rupture of membranes (Caulfield 1998) as well as with growth retardation, congenital abnormalities and retarded neurobehavioral and immunological development in the fetus (Black 2001). Ramakrishnan 1999 states that there is strong evidence primarily from high-income countries that zinc, calcium and magnesium supplementation could improve birthweight, prematurity and hypertension particularly in high-risk groups. Improving maternal iron intake during pregnancy has been shown in Peru to improve the iron status of newborns (O'Brien 2003).

When multiple supplements were provided to HIV-positive pregnant women in Tanzania, the risk of low birthweight decreased by 44% and by 39% for preterm births (Fawzi 1998). There is a published review assessing the effect of micronutrient supplementation in HIV-infected children and adults (Irlam 2005). Daily supplements of vitamin A (retinol) with iron (elemental iron) increased haemoglobin and had a greater impact on reducing anaemia in pregnant women in Indonesia than iron alone (Suharno 1992; Suharno 1993). While absorption of both zinc and iron are inhibited when combined (O'Brien 2003), improvements in both iron and zinc status were found among pregnant women receiving supplements in Peru (Caulfield 1997). It was shown by Scholl that the risk of low birthweight was reduced approximately two-fold with multivitamin supplement use during the first and second trimester of pregnancy although it appeared that this effect was due to an associated two-fold reduction in the risk of preterm delivery. On the other hand, a large Hungarian trial of micronutrient supplementation (Czeizel 1996) found no significant effect on the rate of fetal deaths, low birthweight and preterm birth in singletons.

Rationale for multi-micronutrient supplementation

Multiple-micronutrient deficiencies often coexist and there is an increased interest in evaluating the benefit of multiple-micronutrient supplements in pregnancy. Consideration that there may be multiple deficiencies in low-income to middle-income countries and that it is difficult to evaluate the effects of all of the potentially important micronutrients, as well as their possible interactions, have lead some to conclude that a multivitamin mineral supplement should be given during pregnancy (UNICEF 1999).

Combining multiple micronutrients in a single delivery mechanism has been suggested as a cost-effective way to achieve multiple benefits (Alnwick 1998; Yip 1997). Moreover, micronutrient deficiencies are known to interact and a greater effect may be achieved by multiple supplementation rather than single nutrient supplementation.

Dosage recommendations

In 1999, the UNICEF/UNU/WHO agreed on the composition of a proposed multi-micronutrient tablet providing one recommended daily allowance of vitamin A, vitamin B1, vitamin B2, niacin, vitamin B6, vitamin B12, folic acid, vitamin C, vitamin D, vitamin E, copper, selenium, iodine; with 30 mg of iron and 15 mg of zinc for pregnant women. However, according to the guidelines provided by the National Research Council in 1989, 15 mg of zinc for pregnant and lactating women is based on a dietary availability of zinc of approximately 20%. If dietary availability is only 10%, as is the case in many low-income to middle-income countries, the nutritional requirements of zinc might be much higher.

The controversy: interactions and side-effects of over-dosage

Some authors have questioned the effectiveness of multi-micronutrient supplements due to possible interactions among nutrients resulting in their impaired absorption (Argiratos 1994). Studies have shown that high doses of iron impair the absorption of zinc and vice versa. The risk of interaction is larger when the nutrients are provided as supplements (Sandstrom 2001). Manganese affects iron absorption in a way that indicates that the intestine cannot differentiate between manganese and iron (Rossander 1991). Similarly, high-dose zinc supplements (50 mg per day for 10 weeks) reduce indices for iron and copper status (Yadrick 1989). Calcium was shown to have an absorption depressing affect on iron absorption (Hallberg 1991).

Vitamin C is a strong promoter of iron absorption from the diet (Hallberg 1986). However, long-term vitamin C supplementation may impair the absorption of copper and thereby counteract the positive effect on iron absorption. However, the effects of vitamin C on copper are not conclusive (Jacob 1987). Vitamin C affects selenium availability both positively and negatively depending on chemical form and dietary conditions (Lavender 1987).

Recent studies suggest that vitamin A and beta-carotene can enhance non-haemal iron absorption. Another issue is that frequencies of supplementation and dose levels may not be compatible (Mason 2001). Supplements may result in excess levels causing harm; for example, high doses of vitamin A in pregnant women increases the risk of teratogenicity. Vitamin E excess in adult humans (Bell 1989) causes impaired leukocyte function, increased bleeding and inhibition of platelet prostaglandin synthesis and of platelet aggregation. Iron deficiency, as well as iron overload, seems to involve a degree of oxidative stress. Vitamin C excess has been reported to cause serious cardiovascular disturbances in iron-overloaded patients (McLaran 1982). High doses of vitamin C (500 mg per day) plus iron can cause certain oxidative base modifications in DNA extracted from leucocytes of healthy human donors (Rehman 1998). However, the significance of this is unknown.

Authors argue that poor pregnancy outcome is the result of a multiplicity of factors and cannot be corrected by "a narrow pharmaceutical shortcut"; instead, they call for an overall improvement in antenatal care and dietary diversification (Gopalan 2002). The effectiveness of already existing worldwide conventional iron or folate supplementation programs for pregnant women has been questioned (Yip 1996). These programs suffer from limited coverage, poor compliance and their limitation to the duration of pregnancy provides an insufficient time period in which to reduce iron deficiency.

Mahomed 1997 concluded from his Cochrane review on folate supplementation in pregnancy that although folate appears to improve haemoglobin levels and folate status, there is not enough evidence to evaluate whether folate supplementation has any effect, beneficial or harmful, on clinical outcomes for mother and baby. Similarly, Van den Broek 2002 has identified the need to carry out further trials to determine whether vitamin A supplements can reduce maternal mortality and morbidity.

Clearly substantial evidence is required before the multi-micronutrient supplementation programs are implemented on a global scale. In this review we are looking at three or more micronutrients. Other relevant information can be found in the trials conducted on individual vitamin and minerals and their effects.

OBJECTIVES

To evaluate the benefits to mother and infant of multiple-micronutrient supplements in pregnancy and to assess the risk of excess supplementation and potential adverse interactions between micronutrients.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All prospective randomised controlled trials evaluating micronutrient supplementation during pregnancy and its effects on the pregnancy outcome, irrespective of language or publication status. Quasi-randomised trials were excluded.

Types of participants

Pregnant women. There was no limit on the age of gestation at the time of enrolment in the study. HIV-positive women were excluded from the review.

Types of intervention

Studies comparing the outcomes of supplementing pregnant women with multiple-micronutrient supplements of three or more micronutrients compared with placebo, or no supplementation, or supplementation with two or less micronutrients. Trials that used less 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 outcome measures

(1) Preterm births (births before 37 weeks of gestation);
(2) small-for-gestational age (as defined by the authors of the trials);
(3) low birthweight (birthweight less than 2500 grams);
(4) premature rupture of membranes;
(5) pre-eclampsia;
(6) miscarriage (loss of pregnancy before 24 weeks of gestation);
(7) maternal mortality;
(8) perinatal mortality.

Secondary outcome measures

(1) Maternal anaemia;
(2) neurodevelopmental delay;
(3) placental abruption;
(4) very preterm births (births before 34 weeks of gestation);
(5) cost of supplementation;
(6) side-effects of supplements;
(7) congenital anomalies (including neural tube defects);
(8) maternal wellbeing or satisfaction;
(9) nutritional status of children.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 December 2005).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
(1) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
(2) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

Details of the search strategies for CENTRAL and MEDLINE, the list of hand searched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Search strategies for identification of studies' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes

are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

We searched reference lists of retrieved articles and key reviews. We contacted experts in the field for additional and ongoing trials.

We did not apply any language restrictions.

METHODS OF THE REVIEW

Study selection and eligibility

One review author screened the titles and abstracts of identified studies to ascertain if they met the inclusion criteria. If uncertain, we retrieved the full text of the study. We obtained the full report of all potentially relevant articles. Two authors independently assessed eligibility using the predefined inclusion and exclusion criteria. We resolved any disagreements by discussion. If these methods failed to clarify any doubts, we attempted to contact the named authors. Excluded studies were tabulated along with the reason for their exclusion. Authors of the review were not blinded to periodical names, author and institution names or study results. Efforts were made to ensure that each trial was entered only once in our review.

Assessment of methodological quality

We assessed the validity of each study using the criteria outlined in the Cochrane Reviewers' Handbook (Alderson 2004). Each trial that was shortlisted by the above-mentioned two authors was screened independently for methodological quality. Both authors used a quality assessment form. Disagreements were resolved by discussion. We assessed each study for quality of allocation of concealment, completeness to follow up and blinding in the assessment of outcome.

(1) Selection bias (randomisation and allocation concealment)

We assigned a quality score for each trial, using the following criteria:
(A) adequate concealment of allocation, such as telephone randomisation, consecutively numbered sealed opaque envelopes;
(B) unclear whether adequate concealment of allocation;
(C) inadequate concealment of allocation, such as open list of random number tables, sealed envelopes.

(2) Performance bias (blinding of participants, researchers and outcome assessment)

We assessed blinding using the following criteria:
(1) blinding of participants (yes/no/unclear);
(2) blinding of caregiver (yes/no/unclear);
(3) blinding of outcome assessment (yes/no/unclear).

(3) Attrition bias (loss to follow up)

We assessed completeness to follow up using the following criteria:
(1) A - less than 5% of participants excluded;
(2) B - 5% to 10% of participants excluded;
(3) C - more than 10% and less than 20% of participants excluded;
(4) D - more than 20% of participants excluded.

We performed a sensitivity analysis for studies that were under each of the defined categories for all three factors.

Data extraction

We designed and pilot tested a data extraction form, subsequently utilized by both authors to collect data. Both authors then compared the abstracted data, enabling us to correct errors and resolve any disagreements. We recorded the required information for each treatment arm, such as participants' characteristics, sample size, description of intervention and its comparator (including dosage, frequency and supplement duration), follow-up period and all the above-mentioned outcomes. There were two cluster-randomised trials included in this review (Christian 2003; Pakistan 2002). In order to extract data from these trials, their authors were contacted for an estimate of intra-cluster correlation (ICC). With the help of ICC estimates, design effects were calculated and the sample sizes of the two trials were reduced to their 'effective sample size'. The effective sample sizes were then incorporated in the review.

We conducted an intention-to-treat analysis; thus, if the number in the outcome group was less than the number originally randomised to that group, we derived the percentage loss to follow up and tabulated these results. For dichotomous outcomes we extracted the number of participants and number of participants who experienced the event; for example, for the outcome 'low birthweight'. No data were available for the continuous outcomes. One author entered and double checked the abstracted data into the Review Manager software (RevMan 2003).

Data analysis

We analysed data using RevMan 2003. We assessed the presence of publication bias by using a 'funnel plot'. For dichotomous data we presented results as summary relative risks with 95% confidence intervals. Heterogeneity was checked by visual inspection of forest plots and by using the I^2 statistic. As there was no heterogeneity among the trials, prespecified subgroup analyses were not undertaken and the fixed-effect model was used to pool the results.

A priori subgroup analyses were:
(1) gestational age at which the supplementation was started;
(2) dosage of the micronutrients in the supplement;
(3) base-line nutritional (including the micronutrient) status of the mother;
(4) micronutrient interactions;
(5) duration of treatment.

Since the World Health Organization recommends use of iron folic acid supplementation in women during pregnancy as a part of routine antenatal care, we also evaluated as

a sub-group comparison, the effect of multiple-micronutrient supplementation versus supplementation with iron folic acid.

DESCRIPTION OF STUDIES

Nine trials (15,378 women) were identified as potentially eligible for inclusion in this review and forty-six trials were excluded.

Excluded studies

Seventeen trials were excluded as they assessed the supplementation of only one micronutrient (Caulfield 1999; Chames 2002; Christian 2001; Garg 1994; Goldenberg 1995; Hillman 1963; Hunt 1983; Hunt 1985; Merialdi 1998; Muslimatun 2001; Robertson 1991; Schmidt 2001; Schmidt 2002; Schmidt 2004; Semba 2001; Suharno 1993; Zavaleta 2000). Seven trials were excluded as they evaluated the supplementation of two micronutrients (Beazley 2002; Harrison 1985; Holly 1955; Marya 1987; Mathan 1979; Suprapto 2002; Tanumihardjo 2002). Two trials evaluated supplementation of various combinations of multiple micronutrients and were hence excluded from the review (Dawson 1987; Dawson 1998). One excluded trial assessed different combinations of three micronutrients (Fleming 1986), another assessed high versus low dose of iron supplementation (Guldholt 1991). Two trials were not randomised controlled trials (Haibin 2001; Menon 1962) and another trial used a cross-over design (Biswas 1984). The objective of this cross-over trial did not serve the purpose of our review and was hence excluded. Seven trials included pregnant women who were HIV-1 infected and were also excluded from the review (Fawzi 1998; Fawzi 2000; Fawzi 2004; Fawzi 2004a; Merchant 2005; Villamor 2002; Villamor 2005). The effect of micronutrient supplementation in HIV-infected children and adults is being assessed in a separate review (Irlam 2005). Four trials were excluded because the outcomes reported were not of interest to the review (An 2001; Hininger 2004; Sood 1975; Thauvin 1992) and two more trials were excluded as they assessed the effect of periconceptional supplementation of micronutrients (Czeizel 1996; ICMR 2000).

See the 'Characteristics of excluded studies' table for more details.

Included studies

A total of 15,378 women participated in the nine included trials (Bangladesh 2002; Christian 2003; Dieckmann 1943; Friis 2004; Guinea-Bissau 2003; Osrin 2005; Pakistan 2002; Ramakrishnan 2003; Tatala 2002), of which two were cluster randomised (Christian 2003; Pakistan 2002). Most of the outcomes were defined in the same way across different trials except for miscarriage, which was defined differently in one trial (Dieckmann 1943) and hence did not allow inclusion of data from this trial. *See* the 'Characteristics of included studies' table for details of included studies.

Participants

The trials included 15,378 women at varying gestational ages, ranging from early pregnancy to 36 weeks of gestation. Pregnant women with a haemoglobin of less than 80 g/L, with a serious medical condition or a complication of pregnancy such as cardiac disease, pneumonia and threatened abortion, were not eligible for inclusion in the trials. One trial (Friis 2004) included a subgroup of pregnant women who were HIV-1 infected but their data have not been included in this review. Baseline characteristics of the participants in the intervention and the control groups were comparable in the included trials except for minor differences in two trials (Friis 2004; Ramakrishnan 2003). In Friis 2004, a higher proportion of primigravidae were found in the placebo group and in Ramakrishnan 2003, there was a higher proportion of single mothers and a lower mean body mass index in the intervention group.

Intervention

Six trials assessed multiple-micronutrient supplementation versus supplementation with two or less micronutrients (Bangladesh 2002; Christian 2003; Dieckmann 1943; Guinea-Bissau 2003; Osrin 2005; Ramakrishnan 2003). Another trial also had a component of nutritional education along with supplementation with two or less micronutrients (Pakistan 2002) whereas two trials assessed multiple-micronutrient supplementation against a placebo (Friis 2004; Tatala 2002). The composition of the multiple-micronutrient supplement was different between the trials. All supplements were given orally to the pregnant women throughout pregnancy from the time of enrolment. However, the duration of supplementation varies as the time of enrolment is different for the trials. Four trials enrolled participants in the first trimester of pregnancy (Bangladesh 2002; Christian 2003; Dieckmann 1943; Ramakrishnan 2003). Two trials enrolled participants in the second trimester (Osrin 2005; Pakistan 2002), another two trials enrolled in both second and third trimester (Friis 2004; Tatala 2002) whereas one trial enrolled pregnant women who were less than 37 weeks of gestation (Guinea-Bissau 2003). Supplementation was given until delivery in most of the trials except for one, in which supplements were given until 12 weeks after a live birth or five weeks after a stillbirth or a miscarriage (Christian 2003).

METHODOLOGICAL QUALITY

The included trials were of variable methodological quality. Participants were truly randomised to the treatment groups with adequate allocation concealment in eight trials (Bangladesh 2002; Christian 2003; Friis 2004; Guinea-Bissau 2003; Osrin 2005; Pakistan 2002; Ramakrishnan 2003; Tatala 2002). In three trials (Bangladesh 2002; Guinea-Bissau 2003; Pakistan 2002), the participants and the outcome assessors were blinded to the treatment allocation. Another three trials showed blinding of the participants, caregivers and the outcome assessors (Christian 2003; Ramakrishnan 2003; Tatala 2002). However, only one trial showed blinding of participants and caregivers (Friis 2004) and it was not stated in the text of two trials (Dieckmann 1943; Osrin 2005).

Loss to follow up was less than 5% in two trials (Christian 2003; Osrin 2005), between 5% to 9.9% in two trials (Bangladesh 2002; Pakistan 2002) and between 10% to 19.9% in one trial (Guinea-Bissau 2003). It was more than 20% in three trials (Friis 2004; Ramakrishnan 2003; Tatala 2002). The method of randomisation, allocation concealment and loss to follow up was not stated in the text of one trial (Dieckmann 1943). Intention-to-treat analysis was used in all of the trials. In this review, an intention-to-treat analysis was conducted for all outcome measures. *See* the 'Characteristics of included studies' table for further details on methodological quality of the included studies.

RESULTS

This review includes data on 15,378 women from nine trials.

Primary outcome measures

When compared with supplementation of two or less micronutrients or no supplementation or a placebo, multiple-micronutrient supplementation resulted in a statistically significant decrease in the number of low birthweight babies (relative risk (RR) 0.83; 95% confidence interval (CI) 0.76 to 0.91) and small-for-gestational-age babies (RR 0.92; 95% CI 0.86 to 0.99). No statistically significant differences were shown for the outcomes of preterm births (RR 0.92; 95% CI 0.82 to 1.04) and perinatal mortality (RR 1.05; 95% CI 0.90 to 1.23). However, when multiple-micronutrient supplementation was compared with iron folic acid supplementation, non-significant differences were shown for all primary outcomes (low birthweight babies RR 0.94; 95% CI 0.83 to 1.06, small-for-gestational-age babies RR 1.04; 95% CI 0.93 to 1.17, preterm births RR 0.88; 95% CI 0.76 to 1.03 and perinatal mortality RR 1.16; 95% CI 0.95 to 1.42).

Secondary outcome measures

Multiple-micronutrient supplementation, when compared with supplementation of two or less micronutrients or no supplementation or a placebo, resulted in a statistically significant decrease in maternal anaemia (RR 0.61; 95% CI 0.52 to 0.71). However, the difference lost statistical significance when multiple-micronutrient supplementation was compared with iron folic acid supplementation alone (RR 1.23; 95% CI 0.82 to 1.83).

A number of prespecified clinically important outcomes could not be assessed due to insufficient data from the included trials. These include placental abruption and congenital anomalies including neural tube defects. Outcomes such as premature rupture of membranes, pre-eclampsia, miscarriage, maternal mortality, neurodevelopmental delay, very preterm births, cost of supplementation, side-effects of supplements, maternal wellbeing or satisfaction and nutritional status of children could also not be assessed due to the non-availability of data.

Sensitivity analysis

Sensitivity analysis was undertaken to study the effect of multiple-micronutrient supplementation on the outcomes preterm births, perinatal mortality and maternal anaemia, by excluding a trial in which method of randomisation, allocation concealment and blinding was not stated in the text (Dieckmann 1943). However, the overall effect estimate and the CI were not sensitive to this change. Similarly, no change was observed in the effect estimate and the CI of the above-mentioned outcomes when the trials with loss to follow up of more than 20% were excluded from the analysis (Friis 2004; Ramakrishnan 2003; Tatala 2002).

DISCUSSION

Whether to use a multiple-micronutrient supplement or two or less micronutrients or none during pregnancy is a very important clinical question due to its effects on the fetus and on the mother. Despite the importance of the issue of supplementation during pregnancy in the presence of a wide array of nutrient deficiencies especially among the women from low-income countries, few studies were found that assessed the effect of a multiple-micronutrient supplementation during pregnancy.

Based on the data from the included studies, multiple micronutrients were found to be more effective in reducing the number of low birthweight and small-for-gestational-age babies and maternal anaemia against supplementation with two or less micronutrients or none or a placebo. Since the World Health Organization recommends use of iron folic acid supplementation in women during pregnancy as a part of routine antenatal care, we also evaluated the effect of multiple-micronutrient supplementation versus supplementation with iron folic acid. Analyses showed no added benefit of multiple-micronutrient supplements on iron folic acid supplementation. These findings are very important but they should be interpreted with caution as they are limited by the small number of studies included. These studies were all undertaken in low-income countries and were methodologically of sound quality.

The risk of excess micronutrient supplementation and potential adverse interactions between the micronutrients could not be assessed in this review due to the non-availability of data from the included trials. A substantial amount of evidence could not be included from four trials (An 2001; Hininger 2004; Sood 1975; Thauvin 1992) as the information regarding the outcomes was not collected in a format that allowed inclusion in the review.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence provided in this review is insufficient to guide a policy change and suggest replacement of routine iron and folate supplementation with a multiple-micronutrient supplement.

A reduction in the number of low birthweight and small-for-gestational-age babies and maternal anaemia, however, has been found with a multiple-micronutrient supplement against supplementation with two or less micronutrients or none or a placebo but these results are limited by the small number of studies available. There is also insufficient evidence to identify adverse effects and to say that excess multiple-micronutrient supplementation during pregnancy is harmful to the mother or the fetus.

Implications for research

Further research is needed to find out whether multiple-micronutrient supplementation during pregnancy against supplementation with two or less micronutrients or none or a placebo produces beneficial maternal or fetal outcomes. Future trials on the topic should also collect data on outcomes, which would allow the assessment of the risk of excess supplementation, potential adverse interactions between the micronutrients and the other outcomes that we failed to assess in this review due to non-availability of data. Future reviews and trials also need to focus their efforts on assessing the variability between the different combinations and dosages of the micronutrients in the supplement and hence their effects on the outcome. Researchers should also make efforts to describe the participants in more detail before enrolment and should undertake long-term follow up of the participants and their children in order to study the long-term effects of multiple-micronutrient supplementation. Bias should also be reduced by adequate randomisation and allocation concealment of the assignment of intervention by achieving blinding of the subjects, providers and the outcome assessors and by minimizing loss to follow up of the participants, in order to produce trials of adequate methodological quality.

POTENTIAL CONFLICT OF INTEREST

None known.

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As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and a referee who is external to the editorial team), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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REFERENCES

References to studies included in this review

Bangladesh 2002 *{unpublished data only}*

Anonymous. Multiple micronutrient supplementation of women during pregnancy. Data on file.

Christian 2003 *{published data only}*

* Christian P, Khatry SK, Katz J, Pradhan EK, LeClerq SC, Shrestha SR, et al. Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: double blind randomised community trial. *BMJ* 2003;**326**:571.

Christian P, Shrestha J, LeClerq SC, Khatry SK, Jiang T, Wagner T, et al. Supplementation with micronutrients in addition to iron and folic acid does not further improve the hematologic status of pregnant women in rural Nepal. *Journal of Nutrition* 2003;**133**:3492–8.

Christian P, West KP Jr, Khatry SK, LeClerq SC, Pradhan EK, Katz J, et al. Effects of maternal micronutrient supplementation on fetal loss and infant mortality: a cluster-randomised trial in Nepal. *American Journal of Clinical Nutrition* 2003;**78**:1194–202.

Dieckmann 1943 *{published data only}*

Dieckmann WJ, Adair FL, Michel H, Kramer S, Dunkle F, Arthur B, et al. Calcium, phosphorus, iron and nitrogen balances in pregnant women. *American Journal of Obstetrics and Gynecology* 1943;**47**:357–68.

Friis 2004 *{published data only}*

Friis H, Gomo E, Nyazema N, Ndhlovu P, Krarup H, Kaestel P, et al. Effect of micronutrient supplementation on gestational length and birth size: a randomized, placebo-controlled, double-blind effective-

ness trial in Zimbabwe. *American Journal of Clinical Nutrition* 2004; **80**:178–84.

Guinea-Bissau 2003 *{unpublished data only}*
Anonymous. Multiple micronutrient supplementation in pregnancy. Data on file.

Osrin 2005 *{published data only}*
Osrin D, Vaidya A, Shrestha Y, Baniya RB, Manandhar DS, Adhikari RK, et al. Effects of antenatal micronutrient supplementation on birthweight and gestational duration in Nepal: double-blind, randomised controlled trial. *Lancet* 2005;**365**:955–62.

Pakistan 2002 *{unpublished data only}*
Anonymous. Multiple micronutrient supplementation in pregnancy. Data on file.

Ramakrishnan 2003 *{published data only}*
* Ramakrishnan U, Gonzalez-Cossio T, Neufeld LM, Rivera J, Martorell R. Multiple micronutrient supplementation during pregnancy does not lead to greater infant birth size than does iron-only supplementation: a randomized controlled trial in a semirural community in Mexico. *American Journal of Clinical Nutrition* 2003;**77**:720–5.

Ramakrishnan U, Neufeld LM, Gonzalez-Cossio T, Villalpando S, Garcia-Guerrra A, Juan R, et al. Multiple micronutrient supplements during pregnancy do not reduce anemia or improve iron status compared to iron-only supplements in semirural Mexico. *Journal of Nutrition* 2004;**134**:898–903.

Tatala 2002 *{published data only}*
Makola D, Ask DM, Tatala SR, Latham MC, Ndossi G, Mehansho H. A micronutrient-fortified beverage prevents iron deficiency, reduces anemia and improves the hemoglobin concentration in pregnant tanzanian women. *Journal of Nutrition* 2003;**133**:1339–46.

* Tatala SR, Ash D, Makola D, Latham M, Ndosi G, Grohn Y. Effect of micronutrient fortified beverage on nutritional anaemia during pregnancy. *East African Medical Journal* 2002;**79**(11):598–603.

References to studies excluded from this review

An 2001
An H, Yin S, Xu Q. Effects of supplementing calcium, iron and zinc on the fetus development and growth during pregnancy. *Zhonghua Yu Fang Yi Xue Za Zhi* 2001;**35**(6):370–3.

Beazley 2002
* Beazley D, Ahokas R, Livingston J, Griggs M, Scroggs A, Sibai B. Effects of vitamin C and E supplementation on total antioxidant status (TAS) and 8-isoprostane (IP) levels is women at high risk for preeclampsia. *American Journal of Obstetrics and Gynecology* 2002; **187**(6 Pt 2):S76.

Beazley D, Livingston J, Kao L, Sibai B. Vitamin C and E supplementation in women at high risk for preeclampsia: a double blind placebo controlled trial. *American Journal of Obstetrics and Gynecology* 2002;**187**(6 Pt 2):S216.

Biswas 1984
Biswas MK, Pernoll MJ, Mabie WC. A placebo controlled comparative trial of various prenatal vitamin formulations in pregnant women. *Clinical Therapeutics* 1984;**6**(6):763–9.

Caulfield 1999
* Caulfield L, Zavaleta N, Figueroa A, Leon Z. Maternal zinc supplementation does not affect birth size or pregnancy duration in Peru. *Journal of Nutrition* 1999;**129**:1563–8.

Caulfield LE, Zavaleta N, Figueroa A. Adding zinc to prenatal iron and folate supplements improves maternal and neonatal zinc status in a Peruvian population. *American Journal of Clinical Nutrition* 1999; **69**:1257–63.

Chames 2002
Chames M, Liu H, Bendich A, Bogden J, Siabi B, Prada J. A randomized trial of calcium supplementation: effects on blood lead levels in pregnancy. *American Journal of Obstetrics and Gynecology* 2002;**187** (6 Pt 2):S137.

Christian 2001
Christian P, Khatry SK, Yamini S, Stallings R, LeClerq SC, Shrestha SR, et al. Zinc supplementation might potentiate the effect of vitamin A in restoring night vision in pregnant Nepalese women. *American Journal of Clinical Nutrition* 2001;**73**:1045–51.

Czeizel 1996
Czeizel AE. Controlled studies of multivitamin supplementation on pregnancy outcomes. *Annals of New York Academy of Sciences* 1993; **678**:266–75.

Czeizel AE. Prevention of congenital abnormalities by periconceptional multivitamin supplementation. *BMJ* 1993;**306**:1645–8.

* Czeizel AE. Reduction of urinary tract and cardiovascular defects by periconceptional multivitamin supplementation. *American Journal of Medical Genetics* 1996;**62**:179–83.

Czeizel AE, Dudas I. Prevention of the first occurrence of neural tube defects by periconceptional vitamin supplementation. *New England Journal of Medicine* 1992;**327**:1832–5.

Czeizel AE, Dudas I, Fritz G, Tecsoi A, Hanck A, Kunovits G. The effect of periconceptional multivitamin -mineral supplementation on vertigo, nausea and vomiting in the first trimester of pregnancy. *Archives of Gynecology and Obstetrics* 1992;**251**:181–5.

Czeizel AE, Dudas I, Metneki J. Pregnancy outcomes in a randomized controlled trial of periconceptional multivitamin supplementation. *Archives of Gynecology and Obstetrics* 1994;**255**:131–9.

Czeizel AE, Metneki J, Dudas I. The effect of preconceptional multivitamin supplementation on fertility. *International Journal of Vitamin and Nutrition Research* 1996;**66**:55–8.

Dawson 1987
Dawson EB, McGanity WJ. Protection of maternal iron stores in pregnancy. *Journal of Reproductive Medicine* 1987;**32**(6):478–87.

Dawson 1998
Dawson EB, Dawson R, Behrens J, DeVora M, McGanity WJ. Iron in prenatal multivitamin / multimineral supplements. *Journal of Reproductive Medicine* 1998;**43**:133–40.

Fawzi 1998
Fawzi WW, Msamanga GI, Spiegelman D, Urassa EJN, McGarth N, Mwakagile D, et al. Randomized controlled trial of the effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV -1 infected women in Tanzania. *Lancet* 1998;**351**:1477–82.

Fawzi 2000

Fawzi WW, Msamanga G, Hunter D, Urassa E, Renjifo B, Mwakagile D, et al. Randomized trial of vitamin supplements in relation to vertical transmission of HIV-1 in Tanzania. *Journal of Acquired Immune Deficiency Syndromes* 2000;**23**(3):246–54.

Fawzi 2004

Fawzi W, Msamanga G, Antelman G, Xu C, Hertzmark E, Spiegelman D, et al. Effect of prenatal vitamin supplementation on lower genital levels of HIV type 1 and interleukin type 1 beta at 36 weeks of gestation. *Clinical Infectious Diseases* 2004;**38**(5):716–22.

Fawzi 2004a

Fawzi WW, Msamanga G, Spiegelman D, Wei R, Kapiga S, Villamor E, et al. A randomised trial of multivitamin supplements and HIV disease progression and mortality. *New England Journal of Medicine* 2004;**351**(1):23–32.

Fleming 1986

Fleming AF, Ghatoura GBS, Harrison KA, Briggs ND, Dunn DT. The prevention of anemia in pregnancy in primigravidae in the guinea savana of Nigeria. *Annals of Tropical Medicine and Parasitology* 1986; **80**(2):211–33.

Garg 1994

Garg HK, Singhal KC, Arshad Z. Effect of oral zinc supplementation on copper and haemoglobin levels in pregnant women. *Indian Journal of Physiology and Pharmacology* 1994;**38**(4):272–6.

Goldenberg 1995

Goldenberg RL, Tamura T, Neggers Y, Copper RL, Johnston KE, DuBard MB, et al. The effect of zinc supplementation on pregnancy outcome. *JAMA* 1995;**274**(6):463–8.

Guldholt 1991

Guldholt IS, Trolle BG, Hvidman LE. Iron supplementation during pregnancy. *Acta Obstetricia et Gynecologica Scandinavica* 1991;**70**:9–12.

Haibin 2001

Haibin AN, Shi'an YIN, Qingmei XU, et al. Effects of calcium, iron and zinc on fetus development and growth during pregnancy. *Chinese Journal of Preventive Medicine* 2001;**35**(6):370–3.

Harrison 1985

Harrison KA, Fleming AF, Briggs ND, Rossiter CE. Growth during pregnancy in Nigerian teenage primigravidae. *British Journal of Obstetrics and Gynaecology* 1985;**92**(Suppl 5):32–9.

Hillman 1963

Hillman RW, Cabaud PG, Nilsson DE, Arpin PD, Tufano RJ. Pyridoxine supplementation during pregnancy. *American Journal of Clinical Nutrition* 1963;**12**:427–30.

Hininger 2004

Hininger I, Favier M, Arnaud J, Faure H, Thoulon JM, Hariveau E, et al. Effects of a combined micronutrient supplementation on maternal biological status and newborn anthropometric measurements: a randomized double-blind, placebo-controlled trial in apparently healthy pregnant women. *European Journal of Clinical Nutrition* 2004;**58**:52–9.

Holly 1955

Holly RG. Anemia in pregnancy. *Obstetrics & Gynecology* 1955;**5**(4): 562–9.

Hunt 1983

* Hunt IF, Murphy NJ, Cleaver AE, Fardji B, Swendseid ME, Coulson AH, et al. Zinc supplementation during pregnancy: effects on selected blood constituents and on progress and outcome of pregnancy in low-income women of Mexican descent. *American Journal of Clinical Nutrition* 1984;**40**:508–21.

Hunt IF, Murphy NJ, Cleaver AE, Fardji B, Swendseid ME, Coulson AH, et al. Zinc supplementation during pregnancy: zinc concentration of serum and hair from low income women of Mexican descent. *American Journal of Clinical Nutrition* 1983;**37**:572–82.

Hunt 1985

Hunt IF, Murphy NJ, Cleaver AE, Fardji B, Swendseid ME, Browdy BL, et al. Zinc supplementation during pregnancy in low-income teenagers of Mexican descent: effects on selected blood constituents and on progress and outcome of pregnancy. *American Journal of Clinical Nutrition* 1985;**42**:815–28.

ICMR 2000

Indian Council of Medical Research (ICMR) Collaborating Centers, Central Technical Co-ordinating Unit. Multicentric study of efficacy of periconceptional folic acid containing vitamin supplementation in prevention of open neural tube defects in India. *Indian Journal of Medical Research* 2000;**112**:206–11.

Marya 1987

Marya RK, Rathee S, Manrow M. Effect of calcium and vitamin D supplementation on toxemia of pregnancy. *Gynecologic and Obstetric Investigation* 1987;**24**:38–42.

Mathan 1979

Mathan VI, Baker SJ, Sood SK, Ramachandran K, Ramalingaswami V. WHO sponsored collaborative studies on nutritional anaemia in India. The effects of ascorbic acid and protein supplementation on the response of pregnant women to iron, pteroylglutamic acid and cyanocobalamin therapy. *British Journal of Nutrition* 1979;**42**:391–8.

Menon 1962

Menon MKK, Rajan L. Prophylaxis of anaemia in pregnancy. *British Journal of Obstetrics and Gynaecology of the British Commonwealth* 1962;**12**:382–9.

Merchant 2005

Merchant AT, Msamanga G, Villamor E, Saathoff E, O'Brien M, Hertzmark E, et al. Multivitamin supplementation of HIV- positive women during preganncy reduces hypertension. *Journal of Nutrition* 2005;**135**(7):1776–81.

Merialdi 1998

Merialdi M, Caulfield LE, Zavaleta N, Figueroa A, DiPietro JA. Adding zinc to prenatal iron and folate tablets improves fetal neurobehavioral development. *American Journal of Obstetrics and Gynecology* 1998;**180**:483–90.

Muslimatun 2001

* Muslimatun S, Schmidt MK, Schultink W, West CE, Hautvast JGAJ, Gross R. Weekly supplementation with iron and vitamin A during pregnancy increases hemoglobin concentration but decreases serum ferritin concentration in Indonesian pregnant women. *Journal of Nutrition* 2001;**131**(1):85–90.

Muslimatun S, Schmidt MK, West CE, Schultink W, Hautvast JGAJ, Karyadi D. Weekly vitamin A and iron supplementation during preg-

nancy increases vitamin A concentration of breast milk but not iron status in Indonesian lactating women. *Journal of Nutrition* 2001;**131**: 2664–9.

Robertson 1991
Robertson JS, Heywood B, Atkinson SM. Zinc supplementation during pregnancy. *Journal of Public Health Medicine* 1991;**13**:227–9.

Schmidt 2001
Schmidt MK, Muslimatun S, West CE, Schultink W, Hautvast JGAJ. Vitamin A and iron supplementation of Indonesian pregnant women benefits vitamin A status of their infants. *British Journal of Nutrition* 2001;**86**:607–15.

Schmidt 2002
Schmidt MK, Muslimatun S, Schultink W, West CE, Hautvast JGAJ. Randomized double blind trial of the effect of vitamin A supplementation of Indonesian pregnant women on morbidity and growth of their infants during the first year of life. *European Journal of Clinical Nutrition* 2002;**56**:338–46.

Schmidt 2004
Schmidt MK, Muslimatun S, West CE, Schultink W, Hautvast JG. Mental and psychomotor development in Indonesian infants of mothers supplemented with vitamin A in addition to iron during pregnancy. *British Journal of Nutrition* 2004;**91**(2):279–85.

Semba 2001
Semba RD, Kumwenda N, Taha TE, Mtimavalya L, Broadhead R, Garrett E, et al. Impact of vitamin A supplementation on anemia and plasma erythropoietin concentrations in pregnant women: a controlled trial. *European Journal of Haematology* 2001;**66**:389–95.

Sood 1975
Sood SK, Ramachandran K, Mathur M, Gupta K, Ramalingaswami V, Swarnbai C, et al. WHO sponsored collaborative study on nutritional anemia in India. *Quarterly Journal of Medicine, New Series XLIV* 1975;**174**:241–58.

Suharno 1993
Suharno D, West CE, Muhilal, Karyadi D, Hautvast JGAJ. Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. *Lancet* 1993;**342**:1325–8.

Suprapto 2002
Suprapto B, Widardo, Suhanantyo. Effects of low-dosage vitamin A and riboflavin on iron-folate supplementation in anaemic pregnant women. *Asia Pacific Journal Of Clinical Nutrition* 2002;**11**(4):263–7.

Tanumihardjo 2002
Tanumihardjo SA. Vitamin A and iron status are improved by vitamin A and iron supplementation in pregnant Indonesian women. *Journal of Nutrition* 2002;**132**:1909–12.

Thauvin 1992
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.

Villamor 2002
Villamor E, Msamanga G, Spiegelman D, Antelman G, Peterson KE, Hunter DJ, et al. Effect of multivitamin and vitamin A supplements on weight gain during pregnancy among HIV-1 infected women. *American Journal of Clinical Nutrition* 2002;**76**:1082–90.

Villamor 2005
Villamor E, Saathoff E, Bosch RJ, Hertzmark E, Baylin A, Manji K, et al. Vitamin supplementation of HIV-infected women improves postnatal child growth. *American Journal of Clinial Nutrition* 2005; **81**(4):880–8.

Zavaleta 2000
Zavaleta N, Caulfield LE, Garcia T. Changes in iron status during pregnancy in Peruvian women receiving prenatal iron and folic acid supplements with or without zinc. *American Journal of Clinical Nutrition* 2000;**71**:956–61.

References to studies awaiting assessment

Kubik 2004
Kubik P, Kowalska B, Laskowska-Klita T, Chelchowska M, Leibschang J. Effect of vitamin-mineral supplementation on the status of some microelements in pregnant women. *Przeglad Lekarski* 2004;**61** (7):764–8.

Ling 1996
Ling CD, Zhang ZJ, Chen ZL. Studies on nutritional effects of traditional Chinese tonics with strengthened nutrients on pregnant women and rats. *Chung-Kuo Chung Hsi i Chieh Ho Tsa Chih* 1996; **16**:270–3.

People's League 1942
People's League of Health. Nutrition of expectant and nursing mothers: interim report. *Lancet* 1942;**2**:10–2.

Peoples League of Health. The nutrition of expectant and nursing mothers in relation to maternal and infant mortality and morbidity. *Journal of Obstetrics and Gynaecology of the British Empire* 1946;**53**: 498–509.

Additional references

Alderson 2004
Alderson P, Green S, Higgins JPT, editors. Cochrane Reviewers' Handbook 4.2.2 [updated March 2004]. In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Allen 1993
Allen L. What is marginal malnutrition and does it affect human functions?. *Nutrition Reviews* 1993;**1**(9):255–67.

Alnwick 1998
Alnwick D. Weekly iodine supplements work. *American Journal of Clinical Nutrition* 1998;**67**(6):1103–4.

Argiratos 1994
Argiratos V, Samman S. The effect of calcium carbonate and calcium citrate on the absorption of zinc in health female subjects. *European Journal of Clinical Nutrition* 1994;**48**(3):198–204.

Bell 1989
Bell EF. Upper limit of vitamin E in infant formulas. *Journal of Nutrition* 1989;**119**:1829–31.

Black 2001
Black RE. Micronutrients in pregnancy. *British Journal of Nutrition* 2001;**85**(Suppl 2):S193–S197.

Botto 2002
Botto LD, Mulinare J, Erickson JD. Occurrence of omphalocele in relation to maternal multivitamin use: a population based study. *Pediatrics* 2002;**109**(5):904–8.

Caulfield 1997
Caulfield LE, Zavaleta N. Serum zinc concentrations in pregnant Peruvian women receiving prenatal iron and zinc supplements. FASEB Journal 1997, issue 3774:A654.

Caulfield 1998
Caulfield L, Zavaleta N, Shankur AH, Merialdi M. Potential contribution of maternal zinc supplementation during pregnancy to maternal and child survival. *American Journal of Clinical Nutrition* 1998; **65**:S499–S508.

Chein 1996
Chein PFW, Khan KS, Arnott N. Magnesium sulphate is the treatment of eclampsia and pre-eclampsia: an overview of the evidence from randomized trials. *British Journal of Obstetrics and Gynaecology* 1996;**103**(11):1085–91.

Dunn 1993
Dunn JT. Iodine supplementation and the prevention of cretinism. *Annals of New York Academy of Sciences* 1993;**678**:158–68.

Gopalan 2002
Gopalan C. Multiple micronutrient supplementation in pregnancy. *Nutrition Reviews* 2002;**60**(5 Pt 2):S2–S6.

Hallberg 1986
Hallberg L, Brune M, Rossander L. Effect of ascorbic acid on iron absorption from different types of meals. Studies with ascorbic acid rich foods and synthetic ascorbic acid given in different amounts with different meals. *Human Nutrition: Applied Nutrition* 1986;**40**: 97–113.

Hallberg 1991
Hallberg L, Brune M, Erlandsson M, Sandberg AS, Rossander-Hulten L. Calcium: effect of different amounts on nonheme and heme iron absorption in humans. *American Journal of Clinical Nutrition* 1991;**53**:112–9.

Huffman 1998
Huffman SL, Baker J, Shumann J, Zehner ER. The case for promoting multiple vitamin/mineral supplements for women of reproductive age in developing countries. The LINKAGES project, www.linkagesproject.org (accessed 26 April 2003).

Irlam 2005
Irlam JH, Visser ME, Rollins N, Siegfried N. Micronutrient supplementation in children and adults with HIV infection. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD003650. DOI:10.1002/14651858.CD003650.pub2.

Jacob 1987
Jacob RA, Skala JH, Omeye ST, Turnlund JR. Effect of varying ascorbic acid intakes on copper absorption and ceruloplasmin levels in young men. *Journal of Nutrition* 1987;**117**:2109–15.

Kirksey 1994
Kirksey A, Wachs TD, Yunis F, Srinath U, Rahmanifar A, McCabe GP, et al. Relation of maternal zinc nutrition to pregnancy outcome and infant development in an Egyptian village. *American Journal of Clinical Nutrition* 1994;**60**:782–92.

Ladipo 2000
Ladipo OA. Nutrition in pregnancy: mineral and vitamin supplements. *American Journal of Clinical Nutrition* 2000;**72**(1):S280–S290.

Lavender 1987
Lavender OA. A global view of human selenium nutrition. *Annual Review of Nutrition* 1987;**7**:227–50.

Leslie 1991
Leslie J. Women's nutrition: the key to improving family health in developing countries?. *Health Policy Plan* 1991;**6**(1):1.

Lumley 2001
Lumley J, Watson L, Watson M, Bower C. Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects. *Cochrane Database of Systematic Reviews* 2001, Issue 3. Art. No.: CD001056. DOI:10.1002/14651858.CD001056.

Mahomed 1997
Mahomed K. Folate supplementation in pregnancy. *Cochrane Database of Systematic Reviews* 1997, Issue 3. Art. No.: CD000183. DOI:10.1002/14651858.CD000183.pub2.

Mason 2001
Mason J, Lotfi M, Dalmiya N, Sethuraman K, Deitchler M. The micronutrient report : current progress and trends in the control of vitamin A, iodine and iron deficiencies. MI/UNICEF/Tulane. Ottawa: International Development Research Center 2001.

McLaran 1982
McLaran CJ, Bett JH, Nye JA, Halliday JW. Congestive cardiomyopathy and haemochromatosis - rapid progression possibly accelerated by excessive ingestion of ascorbic acid. *Australian and New Zealand Journal of Medicine* 1982;**12**:187–8.

O'Brien 2003
O'Brien KO, Zavaleta N, Caulfield LE, Yang D-X, Abrams SA. Maternal iron status influences iron transfer to the fetus. *American Journal of Clinical Nutrition* 2003;**77**(4):924–30.

Ramakrishnan 1999
Ramakrishnan U, Manjrekar R, Rivera J, Gonzalez T, Martorell R. Micronutrients and pregnancy outcome. *Nutrition Research* 1999;**19** (1):103–59.

Rehman 1998
Rehman A, Collis CS, Yang M, Kelly M, Diplock AT, Halliwell B, et al. The effect of iron and vitamin C co-supplementation on oxidative damage to DNA in healthy volunteers. *Biochemical Biophysics Research Communications* 1998;**246**(1):293–8.

RevMan 2003
The Cochrane Colloboration. Review Manager (RevMan). 4.2 for Windows. Oxford, England: The Cochrane Colloboration, 2003.

Rossander 1991
Rossander-Hultan L, Brune M, Sandstrom B, Lounerdal B, Hallberg L. Competitive inhibition of iron absorption by manganese and zinc in humans. *American Journal of Clinical Nutrition* 1991;**54**:152–6.

Sandstrom 2001
Sandstrom B. Micronutrient interactions: effects on absorption and bioavailability. *British Journal of Nutrition* 2001;**85**(2):S181–S185.

Stoltzfus 1995
Stoltzfus RJ. Iron deficiency and strategies for its control. Report prepared for the Office of Nutrition. USAID 1995.

Stoltzfus 1997
Stoltzfus RJ, Dreyfuss M, Shrestha JB, Khatry SK, Schultze K, West KP. Effect of maternal vitamin A or beta-carotene supplementation

on iron deficiency anaemia in Nepalese pregnant women, post partum women and infants. Report of the XVIII International Vitamin A Consultative Group (IVACG) meeting; 1997 September; Cairo, Egypt. 1997:28.

Suharno 1992
Suharno D, West CE, Muhilal, Logman MH, de Waart FG, Karyadi D, et al. Cross-sectional study on the iron and vitamin A status of pregnant women in West Java, Indonesia. *American Journal of Clinical Nutrition* 1992;**56**:988–93.

UNICEF 1998
UNICEF. State of the world's children 1998. www.UNICEF.org (accessed 26 April 2003).

UNICEF 1999
UNICEF. Composition of a multi-micronutrient supplement to be used in pilot progrmmes among pregnant women in developing countries 1999. www.UNICEF.org (accessed 25 April 2003).

Van den Broek 2002
Van den Broek N, Kulier R, Gülmezoglu AM, Villar J. Vitamin A supplementation during pregnancy. *Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD001996. DOI: 10.1002/14651858.CD001996.

West 1997
West KP, Khatry SK, Katz J, LeClercq SC, Pradhan EK, Shresta SR, et al. Impact of weekly supplementation with vitamin A or beta carotene on foetal, infant and maternal mortality. Report of the XVIII International Vitamin A Consultative Group (IVACG) meeting; 1997 September; Cairo, Egypt. 1997:28.

West 1999
West KP, Katz J, Khatry SK, LeClerq SC, Pradhan EK, Shrestha SR, et al. Double blind, cluster randomized trial of low dose supplementation with vitamin A or ß-carotene on mortality related to pregnancy in Nepal. *BMJ* 1999;**318**:570–5.

Yadrick 1989
Yadrick MK, Kenney MA, Winterfeldt EA. Iron, copper and zinc status: response to supplementation with zinc or zinc and iron in adult females. *American Journal of Clinical Nutrition* 1989;**49**:145–50.

Yip 1996
Yip R. Iron supplementation during pregnancy: is it effective?. *American Journal of Clinical Nutrition* 1996;**63**:853–5.

Yip 1997
Yip R. Nutrition intervention for the reduction of maternal mortality: evidence to support multiple micronutrient supplementation during pregnancy. Safe motherhood technical consultation; 1997 Oct 18-23 Colombo, Sri Lanka. 1997.

* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Bangladesh 2002**
Methods	This study was conducted in Bangladesh. Randomisation was undertaken by computer-generated block (n= 12) randomisation. Allocation concealment was undertaken by coding pill bottles. Participants and outcome assessors were blinded to the treatment assignment. Loss to follow up was between 5%-10%.
Participants	Pregnant women with gestational age less than 14 weeks, haemoglobin greater than equal to 80 g/L and no serious disease were eligible for enrolment. A total of 3737 women were randomised to three groups, multiple-micronutrient group n = 1224, 60 mg iron 400 mcg folic acid group n = 1265 and 30 mg iron 400 mcg folic acid group n = 1248. There was no significant difference in baseline characteristics between randomisation groups.
Interventions	Multiple-micronutrient group received vitamin A 800 mcg, D 200 IU, E 10 mg, C 70 mg, B1 1.4 mg, B2 1.4 mg, niacin 18 mg, B6 1.9 mg, B12 2.6 mg, folic acid 400 mcg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 mcg and iodine 150 mcg, while the other group received folic acid and iron (60 mg iron 400 mcg folic acid n = 1265 and 30 mg iron 400 mcg folic acid n = 1248).
Outcomes	Size at birth, gestational age at birth, perinatal mortality and maternal haemoglobin.
Notes	We will compare MMN group with the two iron + folic acid groups. Iron folic acid given to all participants. There is virtually no malaria and HIV-1 but diarrhoeal diseases are common. Maternal malnutrition is prevalent.
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**Christian 2003**
Methods	This cluster-randomised trial was carried out in rural Nepal from December 1998 to April 2001. Randomisation was done in blocks of 5 within each village development community by drawing numbered identical chips from a hat. Allocation concealment was undertaken by locking the code allocation in the Johns Hopkins University. The participants, providers and the assessors were blinded to the drug regimens. The per cent loss to follow up was less than 5%.
Participants	A total of 4926 pregnant women were enrolled in the study. The women were randomised into 5 groups as follows: group 1 (n = 941), group 2 (n = 957), group 3 (n = 999), group 4 (n = 1050) and group 5 (n = 1051). Women who were currently pregnant or those who were breastfeeding an infant less than 9 months old were excluded from the study. Also excluded were menopausal, sterilized or widowed women. Baseline characteristics did not differ significantly among the various randomisation groups except for ethnicity and land holding.
Interventions	Group 1 received folic acid 400 ug and vitamin A, group 2 received folic acid 400 ug, iron 60 mg as ferrous fumerate and vitamin A, group 3 contained the same minerals as group 2 in addition to 30 mg of zinc as zinc sulphate, group 4 received similar micronutrients as group 3 in addition to vitamin D 10 ug, vitamin E 10 mg, vitamin B1 1.6 mg, vitamin B2 1.8 mg, niacin 20 mg, vitamin B6 2.2 mg, vitamin B12 2.6 ug, vitamin C 100 mg, vitamin K 65 ug, copper 2 mg and magnesium 100 mg. The control received 1000 ug of vitamin A only. All supplements were given orally from the time of pregnancy detection till 12 weeks after a live birth or 5 weeks after a still birth or a miscarriage.
Outcomes	Preterm births, small-for-gestational age, low birthweight, side-effects, fetal loss, perinatal mortality, neonatal mortality, 3 month infant mortality.
Notes	All women were offered two 400 mg single dose albendazole in the second and third trimester of pregnancy because of the high prevalence of hookworm infestation in this population. Hookworm infestation and vitamin A deficiency are one of the major causes of anaemia in this population. Due to this reason, vitamin A was given to all the participants including the control group. For the purpose of the review, the multiple-micronutrient group includes groups 2, 3 and 4 whereas the control group includes groups 1 and 5.
Allocation concealment	A – Adequate

Study	**Dieckmann 1943**
Methods	The study was carried out by the Department of Obstetrics and Gynecology, The University of Chicago and the Chicago Lying-in Hospital, USA. The groups were selected at random. The methods used for allocation concealment, blinding and percentage loss to follow up were not stated in the text.
Participants	A total of 554 women were randomised into 4 groups, group 1 control (n = 175, mean age = 25.5), group 2 received a cereal containing calcium, phosphorus and iron (n = 179, mean age = 25.5), group 3 received vitamin A and D (n = 98, mean age = 25.3) whereas group 4 received cereal along with vitamin A and D (n = 102, mean age = 24.4). These groups received treatment throughout pregnancy. The groups were comparable at baseline.
Interventions	Intervention group (groups 2 and 4) received 100 gm of cereal containing calcium 0.78 gm, phosphorus 0.62 gm and iron 30 mg, but, on an average, 30-50 gm of cereal was consumed each day. The women were also given vitamin A 39,900 IU and vitamin D 5500 IU daily. Other group (groups 1 and 3) is the control.
Outcomes	Haemoglobin, serum calcium, phosphorus and protein, preterm birth, toxemia in pregnancy, pregnancy loss, perinatal mortality, anemia and placental abruption.
Notes	For the purpose of the review, MMN group includes groups 2 and 4 whereas the control group includes groups 1 and 3.
Allocation concealment	D – Not used

Characteristics of included studies (*Continued*)

Study	**Friis 2004**
Methods	This trial was carried out in Zimbabwe in 1996-1997. Participants were allocated treatment by using simple block randomisation. The digits 0-5 in a computer-generated random sequence were replaced by 6 preassigned permuted blocks of 4: AABB, ABAB, ABBA, BABA, BBAA and BAAB. Digits 6-9 were deleted. Multi-micronutrient and placebo tablets were coded A and B, respectively and the codes were sealed in envelopes. Duplicate containers corresponding to the random sequence, were consecutively numbered from 1 to 1800. The participants were also numbered consecutively at recruitment. The study participants and the providers were blinded but blinding of investigators is unclear. Loss to follow up was more than 20%.
Participants	Pregnant women who were between 22 and 36 weeks of gestation were eligible for enrolment. Participants 1669 were randomised into two groups, multi-micronutrient group n = 837 and placebo n = 832. Out of the 1106 women that were followed, 725 were HIV+ve and 360 were HIV-ve. The intervention and the placebo groups were comparable at baseline except for the higher proportion of primigravida in the placebo group.
Interventions	Multi-micronutrient group received daily supplementation of vitamin A 3000 mcg RE, beta carotene 3.5 mg, thiamine 1.5 mg, riboflavin 1.6 mg, B6 2.2 mg, B12 4 mcg, niacin 17 mg, C 80 mg, D 10 mcg, E 10 mg, zinc 15 mg, copper 1.2 mcg and selenium 65 mcg while the other group received a placebo. An iron folic acid supplement was given separately as part of the routine antenatal care and was not part of the multi-micronutrient tablet. Tablets were given from the day of enrolment until delivery.
Outcomes	Gestational age, birthweight, birth length, head circumference, preterm delivery, low birthweight, IUGR-LBW.
Notes	Study intervention was approximately the RDA for pregnant or lactating women, except for vitamin A for which a higher amount was given. Out of 1106 women that were followed, 725 were HIV-ve whereas 360 were HIV+ve and HIV status of 21 was indeterminate. We will use data of HIV-ve women only, as previously decided by the authors.
Allocation concealment	A – Adequate

Study	**Guinea-Bissau 2003**
Methods	This study was conducted in Guinea-Bissau. Block (n = 150) randomisation was undertaken by drawing of envelopes containing coloured pieces of paper. Allocation concealment was undertaken by colour-coded bottles of pills. Participants and outcome assessors were blinded to the treatment assignment. Loss to follow up was between 10%-20%.
Participants	Pregnant women with less than 37 weeks of gestation were eligible for enrolment. A total of 2100 women were randomised into three groups, multiple-micronutrient RDA group n = 695, multiple-micronutrient 2 RDA group n = 697 and 60 mg iron 400 mcg folic acid group n = 708. There was no significant difference in baseline characteristics between randomisation groups.
Interventions	Fifteen micronutrients were included in the supplement at RDA level, except for folic acid that was included at 400 mcg level. Supplement consisted of vitamin A 800 mcg, D 200 IU, E 10 mg, C 70 mg, B1 1.4 mg, B2 1.4 mg, niacin 18 mg, B6 1.9 mg, B12 2.6 mg, folic acid 400 mcg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 mcg and iodine 150 mcg. Intervention group (n = 1392) received multiple-micronutrient supplements (supplement RDA n = 695, supplement 2 RDA n = 697) while the other group received folic acid 400 mcg and iron 60 mg.
Outcomes	Size at birth, gestational age at birth, perinatal mortality and maternal haemoglobin.
Notes	Malaria is endemic but HIV prevalence is relatively low. Iron folic acid given to all participants.
Allocation concealment	A – Adequate

Study	**Osrin 2005**
Methods	This study was undertaken in Nepal. Randomisation was done in advance of recruitment by allocating participants identification numbers by computer. Allocation concealment was adequate as the allocation was

	done at the trial's office (Katmandu) by a team member who was otherwise uninvolved in the trial. The allocation codes were kept in file in Katmandu and London. It is not mentioned in the text whether blinding was used or not. Loss to follow up was less than 5%.
Participants	Women were eligible for enrolment if an ultrasound examination confirmed a singleton pregnancy, a gestational age between 12 to 20 completed weeks, no notable fetal abnormality, no existing maternal illness of a severity that could compromise the outcome of pregnancy; and that the participant lived in an area of Dhanusha or the adjoining district of Mohattari accessible for home visits. Participants received supplements throughout pregnancy until delivery. Both groups of participants were comparable at baseline.
Interventions	The multi-micronutrient group (n = 600) received tablets containing vitamin A 800 ug, vitamin E 10 mg, vitamin D 5 ug, B1 1.4 mg, B2 1.4 mg, niacin 18 mg, B6 1.9 mg, B12 2.6 ug, folic acid 400 ug, vitamin C 70 mg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 ug, and iodine 150 ug. Control group (n = 600) received tablets containing iron 60 mg and folic acid 400 ug. There were 2 prespecified deviations from the protocol: if a participant's enrolment blood haemoglobin concentration was less than 70 g/L, she was given an extra 60 mg of iron daily, anthelmintic treatment, and her haemoglobin was rechecked after 1 month; and if a participant described night blindness at any time, she was given 2000 ug of vitamin A daily and referred for medical follow up.
Outcomes	Birthweight, gestational duration, miscarriage, stillbirth, early and late neonatal death, infant length and head circumference.
Notes	
Allocation concealment	A – Adequate

Study	**Pakistan 2002**
Methods	This cluster-randomised trial was conducted in Pakistan. Treatments were randomly allocated to 12 urban and 16 rural clusters. Allocation concealment was undertaken by coding pill bottles. Participants and outcome assessors were blinded to the treatment assignment. Loss to follow up was between 5%-9.9%.
Participants	Pregnant women with gestational age 12-20 weeks were eligible for enrolment. 2763 women were randomised into 4 multiple-micronutrient groups (n = 669), iron folic acid group (n = 660), MMN + nutritional education (n = 660) and iron folic acid + nutritional education (n = 774).
Interventions	Multiple-micronutrient group received vitamin A 800 mcg, D 200 IU, E 10 mg, C 70 mg, B1 1.4 mg, B2 1.4 mg, niacin 18 mg, B6 1.9 mg, B12 2.6 mg, folic acid 400 mcg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 mcg and iodine 150 mcg. Iron folic acid groups received 60 mg iron and 400 mcg folic acid.
Outcomes	Size at birth, gestational age at birth, perinatal mortality and maternal haemoglobin.
Notes	MMN and MMN + nutritional education groups were compared with iron folic acid and iron folic acid + nutritional education group. Iron folic acid given to all participants. Maternal malnutrition, vitamin A deficiency, anaemia and iron deficiency are common.
Allocation concealment	A – Adequate

Study	**Ramakrishnan 2003**
Methods	This randomised controlled trial was carried out during 1997-2000 in Mexico. The participants were randomised by using computer-generated randomisation and allocation concealment was performed by using color-coded groups. The participants, providers and the outcome assessors were blinded to the treatment assignment. 217 out of the original 873 randomised pregnancies were loss to follow up (more than 20%).
Participants	Pregnant women who were less than 13 weeks' pregnant, were not receiving multiple-micronutrient supplementation and who agreed to participate were included in the study. A total of 873 women were randomised into the multiple-micronutrient group (n = 435, mean age 23.09 +/- 5.48) and the iron only group (n = 438, mean age 23.00 +/- 5.08). The two groups did not differ significantly in most of the characteristics at recruitment, except for marital status (more single mothers in multiple-micronutrient supplementation group) and mean body mass index (significantly lower in the multiple-micronutrient supplementation group).

Interventions	Multi-micronutrient tablets included the following vitamins and minerals: iron 60 mg as ferrous sulphate, folic acid 215 ug, vitamin A 2150 IU, vitamin D3 309 IU, vitamin E 5.73 IU, thiamin 0.93 mg, riboflavin 1.87 mg, niacin 15.5 mg, vitamin B6 1.94 mg, vitamin B12 2.04 ug, vitamin C 66.5 mg, zinc 12.9 mg, magnesium 252 mg. The controls were given iron only tablets with 60 mg of iron as iron sulphate. All were given orally, from recruitment 6 days a week until delivery.
Outcomes	Preterm births, small-for-gestational age, low birthweight, perinatal mortality, mean haemoglobin concentration, mean serum ferritin.
Notes	Data on birth outcomes were only available for 656 pregnancies (multiple micronutrient group n = 328 and control group, iron only n = 326).
Allocation concealment	A – Adequate

Study	**Tatala 2002**
Methods	The study was conducted in Tanzania. Participant enrolment took place during 2 weeks in August of 1999 and post-intervention evaluations were conducted 8 weeks after enrolment. Participants were allocated to one of the either groups by undertaking block randomisation (10 subjects in each block). Allocation concealment was undertaken by applying codes. Participants, providers and investigators were blinded to the treatment allocation. Loss to follow up was more than 20%.
Participants	Pregnant women between 12-34 weeks of gestation were eligible for enrolment. Exclusion criteria included a pregnancy that was determined to be less than 12 weeks or more than 34 weeks on uterine palpation, a hemoglobin concentration of less than 80 g/L or a serious medical condition, or a complication of pregnancy such as cardiac disease, pneumonia and threatened abortion. The intervention and the placebo groups were comparable at baseline.
Interventions	Micronutrient supplement (n = 227) included iron 10.8 mg, vitamin A 1050 RE, iodine 90 mcg, zinc 10.5 mg, vitamin C 14 mg, riboflavin 1.2 mg, folic acid 280 mcg, vitamin B 12 6 mcg, vitamin B 6 1.4 mg, niacin 10 mg and vitamin E 21 mg. The control group (n = 212) received a placebo.
Outcomes	Anaemia, iron-deficiency anaemia, change in hemoglobin, vitamin A status and thyroid stimulating hormone.
Notes	Malaria is endemic. Intestinal helminth infections are common. All women received elemental iron 60 mg and folic acid 500 mcg. Women who were found to have parasitic infection were treated with a single dose to albendazole 400 mg.
Allocation concealment	A – Adequate

IU: international unit
IUGR: intrauterine growth retardation
LBW: low birthweight
MMN: multiple micronutrient
RDA: recommended daily allowance

Characteristics of excluded studies

Study	**Reason for exclusion**
An 2001	None of the outcomes reported are of interest to the review.
Beazley 2002	Assesses vitamin C and E supplementation only.
Biswas 1984	Cross-over design, measuring only serum iron levels after single doses of different vitamin formulations. Does not serve the purpose of the study.
Caulfield 1999	Only assesses zinc supplementation.
Chames 2002	Only assesses calcium supplementation.

Christian 2001	Only assesses zinc supplementation.
Czeizel 1996	Assesses periconceptional supplementation of 18 micronutrients against 4 micronutrients.
Dawson 1987	Assesses supplementation of 14 micronutrients against 11 micronutrients.
Dawson 1998	Assesses supplementation of different doses of 12 to 17 micronutrients.
Fawzi 1998	Includes pregnant women who are HIV-1 positive.
Fawzi 2000	Includes pregnant women who are HIV-1 positive.
Fawzi 2004	Includes pregnant women who are HIV-1 positive.
Fawzi 2004a	Includes pregnant women who are HIV-1 positive.
Fleming 1986	Only assesses iron, folate and vitamin B in different combinations.
Garg 1994	Only assesses zinc supplementation.
Goldenberg 1995	Only assesses zinc supplementation.
Guldholt 1991	Only assesses high-dose versus low-dose iron supplementation.
Haibin 2001	Not a RCT.
Harrison 1985	Only assesses iron and folate supplementation.
Hillman 1963	Only assesses pyridoxine supplementation.
Hininger 2004	None of the outcomes reported are of interest to this review.
Holly 1955	Only assesses iron and cobalt supplementation.
Hunt 1983	Only assesses zinc supplementation.
Hunt 1985	Only assesses zinc supplementation.
ICMR 2000	Assesses periconceptional supplementation of folic acid containing vitamins.
Marya 1987	Only assesses calcium and vitamin D supplementation.
Mathan 1979	Assesses supplementation of vitamin C and protein.
Menon 1962	Not a RCT.
Merchant 2005	Includes pregnant women who are HIV-1 positive.
Merialdi 1998	Only assesses zinc supplementation.
Muslimatun 2001	Only assesses vitamin A supplementation.
Robertson 1991	Only assesses zinc supplementation.
Schmidt 2001	Only assesses vitamin A supplementation.
Schmidt 2002	Only assesses vitamin A supplementation.
Schmidt 2004	Only assesses vitamin A supplementation.
Semba 2001	Only assesses vitamin A supplementation.
Sood 1975	None of the outcomes reported are of interest to this review.
Suharno 1993	Only assesses vitamin A supplementation.
Suprapto 2002	Only assesses vitamin A and riboflavin supplementation.
Tanumihardjo 2002	Only assesses vitamin A and iron supplementation.
Thauvin 1992	None of the outcomes reported are of interest to this review.
Villamor 2002	Includes pregnant women who are HIV-1 positive.
Villamor 2005	Includes pregnant women who are HIV-1 positive.
Zavaleta 2000	Only assesses zinc supplementation.

RCT: randomised controlled trial

Characteristics of excluded studies (*Continued*)

ANALYSES

Comparison 01. Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Preterm births			Relative Risk (Fixed) 95% CI	Subtotals only
02 Small-for-gestational age	2	2826	Relative Risk (Fixed) 95% CI	0.92 [0.86, 0.99]
03 Low birthweight			Relative Risk (Fixed) 95% CI	Subtotals only
08 Perinatal mortality			Relative Risk (Fixed) 95% CI	Subtotals only
09 Anaemia			Relative Risk (Fixed) 95% CI	Subtotals only
11 Placental abruption	1	554	Relative Risk (Fixed) 95% CI	0.49 [0.04, 5.33]
15 Congenital anomalies including neural tube defects	1	1106	Odds Ratio (Fixed) 95% CI	0.99 [0.14, 7.05]

Comparison 02. Multiple micronutrients versus iron folate only

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Preterm births	4	3669	Relative Risk (Fixed) 95% CI	0.88 [0.76, 1.03]
02 Small-for-gestational age	2	2018	Relative Risk (Fixed) 95% CI	1.04 [0.93, 1.17]
03 Low birthweight	4	3576	Relative Risk (Fixed) 95% CI	0.94 [0.83, 1.06]
04 Perinatal mortality	5	6603	Relative Risk (Fixed) 95% CI	1.16 [0.95, 1.42]
05 Anaemia	1	347	Relative Risk (Fixed) 95% CI	1.23 [0.82, 1.83]
06 Congenital anomalies including neural tube defects	1	1106	Odds Ratio (Fixed) 95% CI	0.99 [0.14, 7.05]

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements [adverse effects]; Drug Interactions; Micronutrients [*administration & dosage; adverse effects]; Pregnancy Complications [*therapy]; Pregnancy Outcome; Randomized Controlled Trials

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Multiple-micronutrient supplementation for women during pregnancy
Authors	Haider BA, Bhutta ZA
Contribution of author(s)	Data extraction was done by Dr Batool A Haider and Dr Zulfiqar A Bhutta. Dr Batool A Haider entered the data, created the comparisons, did the analysis and wrote the text of the review. Dr Zulfiqar A Bhutta provided support and guidance for the review.
Issue protocol first published	2004/3
Review first published	2006/4
Date of most recent amendment	21 August 2006
Date of most recent SUBSTANTIVE amendment	08 August 2006
What's New	Information not supplied by author

Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	30 December 2005
Date authors' conclusions section amended	Information not supplied by author
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Editorial group code	HM-PREG

GRAPHS AND OTHER TABLES

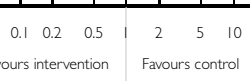
Analysis 01.01. Comparison 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients), Outcome 01 Preterm births

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients)

Outcome: 01 Preterm births

Study	Intervention n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 All trials					
Christian 2003	280/1320	186/875		50.5	1.00 [0.85, 1.18]
Dieckmann 1943	6/281	8/273		1.8	0.73 [0.26, 2.07]
Friis 2004	46/364	58/361		13.1	0.79 [0.55, 1.13]
Osrin 2005	47/571	54/568		12.2	0.87 [0.60, 1.26]
Pakistan 2002	59/233	84/268		17.6	0.81 [0.61, 1.07]
Ramakrishnan 2003	24/321	21/321		4.7	1.14 [0.65, 2.01]
Subtotal (95% CI)	3090	2666		100.0	0.92 [0.82, 1.04]
Total events: 462 (Intervention), 411 (Control)					
Test for heterogeneity chi-square=3.34 df=5 p=0.65 I^2 =0.0%					
Test for overall effect z=1.31 p=0.2					
02 'A' quality trials					
Christian 2003	280/1320	186/875		51.4	1.00 [0.85, 1.18]
Friis 2004	46/364	58/361		13.4	0.79 [0.55, 1.13]
Osrin 2005	47/571	54/568		12.4	0.87 [0.60, 1.26]
Pakistan 2002	59/233	84/268		18.0	0.81 [0.61, 1.07]
Ramakrishnan 2003	24/321	21/321		4.8	1.14 [0.65, 2.01]
Subtotal (95% CI)	2809	2393		100.0	0.93 [0.82, 1.05]
Total events: 456 (Intervention), 403 (Control)					
Test for heterogeneity chi-square=3.14 df=4 p=0.53 I^2 =0.0%					
Test for overall effect z=1.24 p=0.2					
03 Trials with loss to follow up more than 20% excluded					
Christian 2003	280/1320	186/875		62.8	1.00 [0.85, 1.18]
Osrin 2005	47/571	54/568		15.2	0.87 [0.60, 1.26]
Pakistan 2002	59/233	84/268		21.9	0.81 [0.61, 1.07]
Subtotal (95% CI)	2124	1711		100.0	0.94 [0.82, 1.07]
Total events: 386 (Intervention), 324 (Control)					
Test for heterogeneity chi-square=1.79 df=2 p=0.41 I^2 =0.0%					
Test for overall effect z=0.97 p=0.3					



Analysis 01.02. Comparison 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients), Outcome 02 Small-for-gestational age

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients)

Outcome: 02 Small-for-gestational age

Study	Intervention n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 All trials ('A' quality)					
Christian 2003	713/1320	510/875		94.3	0.93 [0.86, 1.00]
Ramakrishnan 2003	32/317	37/314		5.7	0.86 [0.55, 1.34]
Total (95% CI)	1637	1189		100.0	0.92 [0.86, 0.99]
Total events: 745 (Intervention), 547 (Control)					
Test for heterogeneity chi-square=0.12 df=1 p=0.73 I^2 =0.0%					
Test for overall effect z=2.10 p=0.04					

Analysis 01.03. Comparison 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients), Outcome 03 Low birthweight

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients)

Outcome: 03 Low birthweight

Study	Intervention n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 All trials ('A' quality)					
Christian 2003	481/1324	373/875		64.7	0.85 [0.77, 0.95]
Friis 2004	26/364	35/361		5.1	0.74 [0.45, 1.20]
Osrin 2005	101/529	133/523		19.3	0.75 [0.60, 0.94]
Pakistan 2002	41/233	52/268		7.0	0.91 [0.63, 1.31]
Ramakrishnan 2003	27/318	28/315		4.1	0.96 [0.58, 1.58]
Subtotal (95% CI)	2768	2342		100.0	0.83 [0.76, 0.91]
Total events: 676 (Intervention), 621 (Control)					
Test for heterogeneity chi-square=1.70 df=4 p=0.79 I^2 =0.0%					
Test for overall effect z=3.91 p=0.00009					
02 Trials with loss to follow up more than 20% excluded					
Christian 2003	481/1324	373/875		71.2	0.85 [0.77, 0.95]
Osrin 2005	101/529	133/523		21.2	0.75 [0.60, 0.94]

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Study	Intervention n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Pakistan 2002	41/233	52/268		7.7	0.91 [0.63, 1.31]
Subtotal (95% CI)	2086	1666		100.0	0.83 [0.76, 0.92]
Total events: 623 (Intervention), 558 (Control)					
Test for heterogeneity chi-square=1.17 df=2 p=0.56 I^2 =0.0%					
Test for overall effect z=3.80 p=0.0001					

Analysis 01.08. Comparison 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients), Outcome 08 Perinatal mortality

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients)

Outcome: 08 Perinatal mortality

Study	Intervention n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 All trials					
Bangladesh 2002	52/1224	114/2513		24.5	0.94 [0.68, 1.29]
Christian 2003	122/1696	84/1153		32.9	0.99 [0.76, 1.29]
Dieckmann 1943	16/379	4/171		1.8	1.80 [0.61, 5.32]
Guinea-Bissau 2003	96/1392	50/708		21.8	0.98 [0.70, 1.36]
Osrin 2005	28/571	23/568		7.6	1.21 [0.71, 2.08]
Pakistan 2002	44/460	31/467		10.1	1.44 [0.93, 2.24]
Ramakrishnan 2003	5/328	4/326		1.3	1.24 [0.34, 4.59]
Subtotal (95% CI)	6050	5906		100.0	1.05 [0.90, 1.23]
Total events: 363 (Intervention), 310 (Control)					
Test for heterogeneity chi-square=4.15 df=6 p=0.66 I^2 =0.0%					
Test for overall effect z=0.67 p=0.5					
02 'A' quality trials					
Bangladesh 2002	52/1224	114/2513		25.0	0.94 [0.68, 1.29]
Christian 2003	122/1696	84/1153		33.5	0.99 [0.76, 1.29]
Guinea-Bissau 2003	96/1392	50/708		22.2	0.98 [0.70, 1.36]
Osrin 2005	28/571	23/568		7.7	1.21 [0.71, 2.08]
Pakistan 2002	44/460	31/467		10.3	1.44 [0.93, 2.24]

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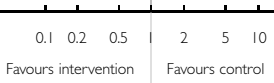
Study	Intervention n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ramakrishnan 2003	5/328	4/326		1.3	1.24 [0.34, 4.59]
Subtotal (95% CI)	5671	5735		100.0	1.04 [0.89, 1.21]
Total events: 347 (Intervention), 306 (Control)					
Test for heterogeneity chi-square=3.17 df=5 p=0.67 I^2 =0.0%					
Test for overall effect z=0.50 p=0.6					
03 Trials with loss to follow up more than 20% excluded					
Bangladesh 2002	52/1224	114/2513		25.3	0.94 [0.68, 1.29]
Christian 2003	122/1696	84/1153		33.9	0.99 [0.76, 1.29]
Guinea-Bissau 2003	96/1392	50/708		22.5	0.98 [0.70, 1.36]
Osrin 2005	28/571	23/568		7.8	1.21 [0.71, 2.08]
Pakistan 2002	44/460	31/467		10.4	1.44 [0.93, 2.24]
Subtotal (95% CI)	5343	5409		100.0	1.04 [0.89, 1.21]
Total events: 342 (Intervention), 302 (Control)					
Test for heterogeneity chi-square=3.10 df=4 p=0.54 I^2 =0.0%					
Test for overall effect z=0.46 p=0.6					



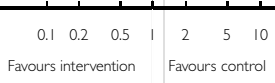
Analysis 01.09. Comparison 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients), Outcome 09 Anaemia

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients)

Outcome: 09 Anaemia

Study	Intervention n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 All trials					
Christian 2003	105/326	131/211		69.2	0.52 [0.43, 0.63]
Dieckmann 1943	9/281	8/273		3.5	1.09 [0.43, 2.79]
Tatala 2002	47/127	64/132		27.3	0.76 [0.57, 1.02]
Subtotal (95% CI)	734	616		100.0	0.61 [0.52, 0.71]
Total events: 161 (Intervention), 203 (Control)					
Test for heterogeneity chi-square=6.58 df=2 p=0.04 I^2 =69.6%					
Test for overall effect z=6.28 p<0.00001					
02 'A' quality trials					



(*Continued* . . .)

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Study	Intervention n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Christian 2003	105/326	131/211		71.7	0.52 [0.43, 0.63]
Tatala 2002	47/127	64/132		28.3	0.76 [0.57, 1.02]
Subtotal (95% CI)	453	343		100.0	0.59 [0.50, 0.69]
Total events: 152 (Intervention), 195 (Control)					
Test for heterogeneity chi-square=4.85 df=1 p=0.03 I^2 =79.4%					
Test for overall effect z=6.60 p<0.00001					

Analysis 01.11. Comparison 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients), Outcome 11 Placental abruption

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients)

Outcome: 11 Placental abruption

Study	Intervention n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Dieckmann 1943	1/281	2/273		100.0	0.49 [0.04, 5.33]
Total (95% CI)	281	273		100.0	0.49 [0.04, 5.33]
Total events: 1 (Intervention), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.59 p=0.6					

Analysis 01.15. Comparison 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients), Outcome 15 Congenital anomalies including neural tube defects

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 01 Multiple micronutrients versus controls (no supplements, placebo or less than two micronutrients)

Outcome: 15 Congenital anomalies including neural tube defects

Study	Intervention n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Osrin 2005	2/556	2/550		100.0	0.99 [0.14, 7.05]
Total (95% CI)	556	550		100.0	0.99 [0.14, 7.05]
Total events: 2 (Intervention), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.01 p=1					

Analysis 02.01. Comparison 02 Multiple micronutrients versus iron folate only, Outcome 01 Preterm births

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 02 Multiple micronutrients versus iron folate only

Outcome: 01 Preterm births

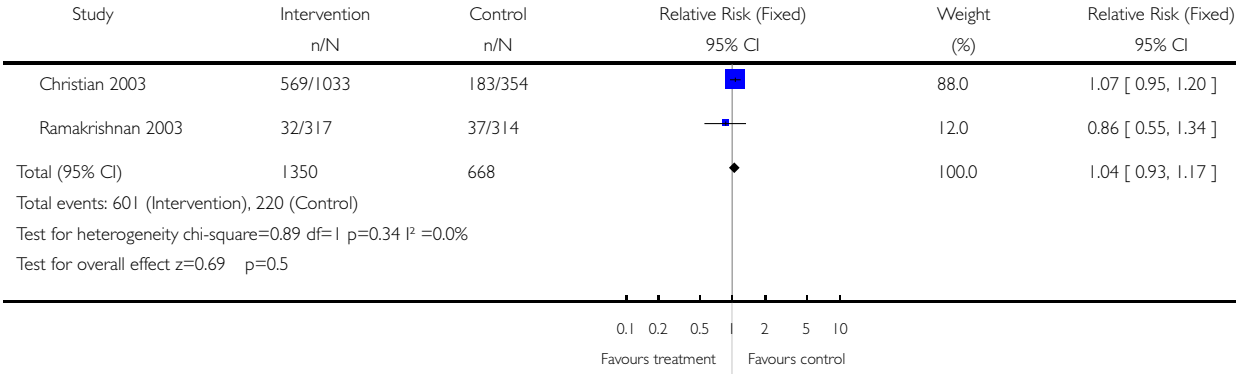
Study	Intervention n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Christian 2003	211/1033	81/354		44.0	0.89 [0.71, 1.12]
Osrin 2005	47/571	54/568		19.8	0.87 [0.60, 1.26]
Pakistan 2002	59/233	84/268		28.5	0.81 [0.61, 1.07]
Ramakrishnan 2003	24/321	21/321		7.7	1.14 [0.65, 2.01]
Total (95% CI)	2158	1511		100.0	0.88 [0.76, 1.03]
Total events: 341 (Intervention), 240 (Control)					
Test for heterogeneity chi-square=1.20 df=3 p=0.75 I^2 =0.0%					
Test for overall effect z=1.59 p=0.1					

Analysis 02.02. Comparison 02 Multiple micronutrients versus iron folate only, Outcome 02 Small-for-gestational age

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 02 Multiple micronutrients versus iron folate only

Outcome: 02 Small-for-gestational age

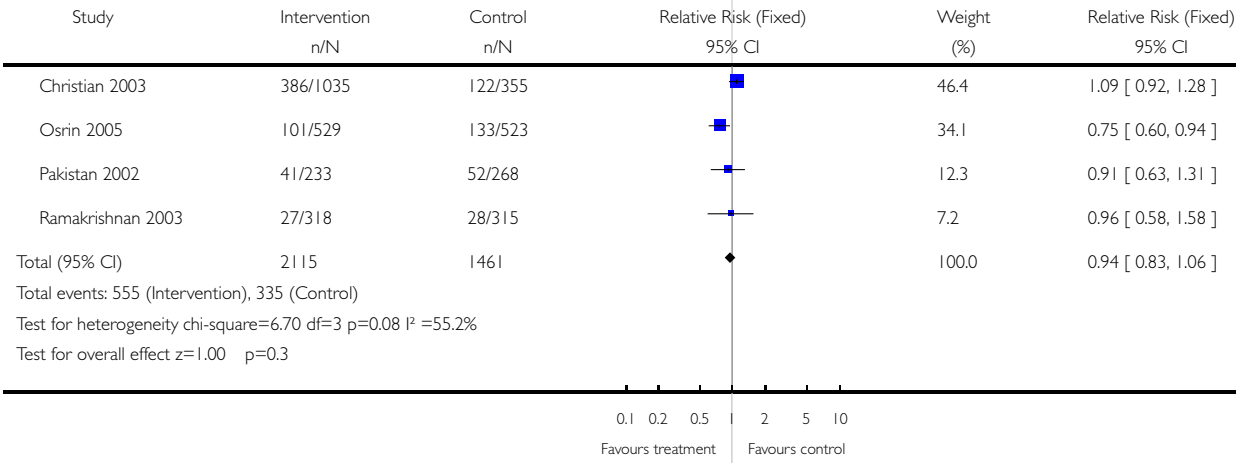


Analysis 02.03. Comparison 02 Multiple micronutrients versus iron folate only, Outcome 03 Low birthweight

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 02 Multiple micronutrients versus iron folate only

Outcome: 03 Low birthweight



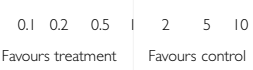
Analysis 02.04. Comparison 02 Multiple micronutrients versus iron folate only, Outcome 04 Perinatal mortality

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 02 Multiple micronutrients versus iron folate only

Outcome: 04 Perinatal mortality

Study	Intervention n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Christian 2003	102/1336	28/447		25.3	1.22 [0.81, 1.83]
Guinea-Bissau 2003	96/1392	50/708		39.9	0.98 [0.70, 1.36]
Osrin 2005	28/571	23/568		13.9	1.21 [0.71, 2.08]
Pakistan 2002	44/460	31/467		18.5	1.44 [0.93, 2.24]
Ramakrishnan 2003	5/328	4/326		2.4	1.24 [0.34, 4.59]
Total (95% CI)	4087	2516		100.0	1.16 [0.95, 1.42]
Total events: 275 (Intervention), 136 (Control)					
Test for heterogeneity chi-square=2.07 df=4 p=0.72 I^2 =0.0%					
Test for overall effect z=1.47 p=0.1					



Analysis 02.05. Comparison 02 Multiple micronutrients versus iron folate only, Outcome 05 Anaemia

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 02 Multiple micronutrients versus iron folate only

Outcome: 05 Anaemia

Study	Intervention n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Christian 2003	92/271	21/76		100.0	1.23 [0.82, 1.83]
Total (95% CI)	271	76		100.0	1.23 [0.82, 1.83]
Total events: 92 (Intervention), 21 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.01 p=0.3					

Analysis 02.06. Comparison 02 Multiple micronutrients versus iron folate only, Outcome 06 Congenital anomalies including neural tube defects

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 02 Multiple micronutrients versus iron folate only

Outcome: 06 Congenital anomalies including neural tube defects

Study	Intervention n/N	Control n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Osrin 2005	2/556	2/550		100.0	0.99 [0.14, 7.05]
Total (95% CI)	556	550		100.0	0.99 [0.14, 7.05]
Total events: 2 (Intervention), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.01 p=1