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[Intervention Review]

Zinc supplementation for improving pregnancy and infant outcome

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ABSTRACT

Background

It has been suggested that low serum zinc levels may be associated with suboptimal outcomes of pregnancy such as prolonged labour, atonic postpartum haemorrhage, pregnancy-induced hypertension, preterm labour and post-term pregnancies, although many of these associations have not yet been established.

Objectives

To assess the effects of zinc supplementation in pregnancy on maternal, fetal, neonatal and infant outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2011) and reference lists of retrieved studies.

Selection criteria

Randomised trials of zinc supplementation in pregnancy. We excluded quasi-randomised controlled trials.

Data collection and analysis

Three review authors applied the study selection criteria, assessed trial quality and extracted data. When necessary, we contacted study authors for additional information.

Main results

We included 20 randomised controlled trials (RCTs) reported in 51 papers involving over 15,000 women and their babies. Trials were generally at low risk of bias. Zinc supplementation resulted in a small but significant reduction in preterm birth (risk ratio (RR) 0.86, 95% confidence interval (CI) 0.76 to 0.97 in 16 RCTs; 16 trials of 7637 women). This was not accompanied by a similar reduction in numbers of babies with low birthweight (RR 0.93, 95% CI 0.78 to 1.12; 14 trials of 5643 women). No significant differences were

seen between the zinc and no zinc groups for any of the other primary maternal or neonatal outcomes, except for induction of labour in a single trial. No differing patterns were evident in the subgroups of women with low versus normal zinc and nutrition levels or in women who complied with their treatment versus those who did not.

Authors' conclusions

The evidence for a 14% relative reduction in preterm birth for zinc compared with placebo was primarily represented by trials involving women of low income and this has some relevance in areas of high perinatal mortality. There was no convincing evidence that zinc supplementation during pregnancy results in other useful and important benefits. Since the preterm association could well reflect poor nutrition, studies to address ways of improving the overall nutritional status of populations in impoverished areas, rather than focusing on micronutrient and or zinc supplementation in isolation, should be an urgent priority.

PLAIN LANGUAGE SUMMARY

Zinc supplementation for improving pregnancy and infant outcome

Taking zinc during pregnancy helps to slightly reduce preterm births, but does not prevent other problems such as low birthweight babies.

Many women of childbearing age may have mild to moderate zinc deficiency. Low zinc concentrations may cause preterm birth or they may even prolong labour. It is also possible that zinc deficiency may affect infant growth as well. This review of 20 randomised controlled trials, involving over 15,000 women and their babies, found that although zinc supplementation has a small effect on reducing preterm births, it does not help to prevent low birthweight babies compared with not giving zinc supplements before 27 weeks' of pregnancy. No clear differences were seen for development of pregnancy hypertension or pre-eclampsia. The 14% relative reduction in preterm birth for zinc compared with placebo was primarily represented by trials of women with low incomes. In some trials all women were also given iron, folate or vitamins or combinations of these. UNICEF is already promoting antenatal use of multiple-micronutrient supplementation, including zinc, to all pregnant women in developing countries. Finding ways to improve women's overall nutritional status, particularly in low-income areas, will do more to improve the health of mothers and babies than supplementing pregnant women with zinc alone. In low-to-middle income countries, addressing anaemia and infections, such as malaria and hookworm, is also necessary.

BACKGROUND

The overall nutritional status of the mother during pregnancy is a significant contributor to both maternal and perinatal mortality and morbidity (Koblinsky 1995). This is likely to be even more crucial in developing countries where anaemia and infections, such as malaria and hookworm, compound the issue even further.

Zinc is known to play an important role in many biological functions, including protein synthesis and nucleic acid metabolism (Valee 1993). Although severe zinc deficiency is now considered rare, mild to moderate deficiency may be relatively common throughout the world (Sanstead 1991). In a review of literature published between 1970 and 1991, Parr 1996 noted that, on average, pregnant and lactating women worldwide consumed 9.6 mg zinc per day, well below the recommended 15 mg daily, during the last two trimesters of pregnancy (Sanstead 1996; WHO 1996). In animal studies, zinc deficiency during the early stages of pregnancy is associated with reduced fertility (Apgar 1970), fetal neurological malformations and growth retardation (McKenzie 1975), and deficiency in later stages of pregnancy negatively affects neuronal growth and may also be associated with impaired brain function and behavioural abnormalities (Golub 1995).

In humans, pregnant women with acrodermatitis enteropathica (an inherited defect in zinc absorption from the bowel) show association with increased risk of congenital malformations and pregnancy losses (Verburg 1974). Numerous reports have noted low serum zinc levels to be linked with abnormalities of labour such as prolonged labour and atonic postpartum haemorrhage (Prema 1980), pregnancy-induced hypertension (Jameson 1976; Jameson 1993), preterm labour (Jones 1981) and post-term pregnancies (Simmer 1985). Others (Cherry 1981; Chesters 1982) have failed

to show any such association.

Some researchers have also reported an association between low zinc and small-for-gestational age babies, and poor perinatal outcome (Kiilholma 1984a; Kiilholma 1984b). Kirksey 1994 reported low maternal serum zinc levels during pregnancy to be associated with an increased risk of low birthweight and preterm birth. Low birthweight babies have higher rates of morbidity and mortality due to infectious disease and impaired immunity and, thus, it is possible that zinc deficiency may affect infant growth and wellbeing too.

Studies of the effects of zinc supplementation have differed in their findings. These inconsistencies in study findings could be due to lack of consensus on accurate assessment of zinc status (Aggett 1991) and to differences in the populations studied. Randomised controlled trials of zinc supplementation in pregnancy would help to address the association, if any, between zinc deficiency and pregnancy outcome and neonatal and infant health and wellbeing.

The fetal nervous system also develops progressively during pregnancy influencing motor and autonomic functions. Change in the pattern of fetal heart rate and movements monitored electronically have been related to fetal neurobehavioural development (DiPietro 1996) and atypical neurodevelopment has been shown in fetuses that exhibit other indicators of neurologic compromise (Hepper 1995). In a publication from Egypt, Kirskey 1991 also reported a positive association between maternal zinc status during the second trimester of pregnancy and newborn behaviour.

It is plausible that the effect of zinc supplementation would vary among different population groups depending on their nutritional status, with any effect likely to be more apparent in women from the developing world. Currently, UNICEF is already promoting antenatal use of multiple-micronutrient supplementation, including zinc, to all pregnant women in developing countries (Nepal 2003).

The aim of this review is to systematically review all randomised controlled trials of zinc supplementation in pregnancy and to evaluate the role of zinc as it relates to pregnancy, labour and birth as well as to maternal and infant health and wellbeing.

OBJECTIVES

1. To compare the effects on maternal, fetal, neonatal and infant outcomes in healthy pregnant women, supplemented with zinc, with those supplemented with either placebo or no zinc.

2. To assess the above outcomes in a subgroup analysis reviewing studies performed in women who are or are likely to be zinc deficient.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials of zinc supplementation versus no zinc supplementation or placebo administration during pregnancy, earlier than 27 weeks' gestation. Quasi-randomised controlled trials have been excluded. We intended to include studies presented only as abstracts, if they provided enough information or, if necessary, by contacting authors to analyse them against criteria; we did not find such studies.

Types of participants

Normal pregnant women with no systemic illness. Women may have had normal zinc levels or they may have been, or likely to have been, zinc deficient.

Types of interventions

Routine zinc supplementation versus no zinc supplementation, or placebo.

Types of outcome measures

We have included outcomes related to clinical complications of pregnancy on maternal, fetal, neonatal and infant outcomes. We have not included data related to biochemical outcomes or studies reporting only biochemical outcomes.

Primary outcomes

Maternal and pregnancy outcomes

Preterm labour or birth (less than 37 weeks), or both

Neonatal outcomes

Stillbirth or neonatal death
Birthweight
Small-for-gestational age (birthweight less than 10th centile for gestational age)
Low birthweight (less than 2.5 kg)

Secondary outcomes

Maternal and pregnancy outcomes

Antepartum haemorrhage
Pregnancy-induced hypertension
Prelabour rupture of membranes
Post-term pregnancy
Induction of labour
Any maternal infection
Meconium in liquor
Caesarean section
Instrumental vaginal birth
Retained placenta
Postpartum haemorrhage
Smell dysfunction
Taste dysfunction

Fetal neurodevelopmental assessment

Baseline fetal heart rate
Baseline variability
Number of accelerations
Number of fetal movements
Fetal activity level (minutes)
Movement amplitude

Neonatal outcomes

Gestational age at birth
High birthweight (more than 4.5 kg)
Apgar score of less than five at five minutes
Head circumference
Hypoxia
Neonatal sepsis
Neonatal jaundice
Respiratory distress syndrome
Neonatal intraventricular haemorrhage
Necrotising enterocolitis
Neonatal length of hospital stay
Congenital malformation (non-prespecified outcome)

Infant/child outcomes

Episodes of disease
Weight for age Z-score
Weight for height Z-score
Mid-upper arm circumference
Mental development index
Psychomotor development index
Other measures of infant or child development

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 September 2011).
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. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We searched the references lists of retrieved studies and identified an unpublished study from a review article (Osendarp 2003).
We did not apply any language restrictions.

Data collection and analysis

For methods used to assess trials included in previous versions of this review, *see* Appendix 1.
The following methods were used to assess China 2001; Ghana 2009; Iran 2010.

Selection of studies

Review authors Rintaro Mori (RM), Erika Ota (EO), and Ruoyan Tobe-Gai (RT) independently assessed for inclusion all the potential studies we identify as a result of the search strategy. We resolved all the disagreements through discussion.

Data extraction and management

We designed a form to extract data. For eligible studies, RM, EO and RT extracted the data using the agreed form. We planned to resolve any discrepancies through discussion or, if required, we would have consulted PM. We entered data into Review Manager software (RevMan 2011) and checked for accuracy.

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

Assessment of risk of bias in included studies

RM, EO and RT independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion. PM and RM independently re-assessed risk of bias using the updated format newly required for all the studies already included in the previous version due to changes in methods (Higgins 2011).

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

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

We assessed the method as:

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

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

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

We assessed the methods as:

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

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

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

We assessed the methods as:

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

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

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

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

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

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

We assessed methods as:

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

(5) Selective reporting (checking for reporting bias)

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

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to

include results of a key outcome that would have been expected to have been reported);

- unclear risk of bias.

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

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

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

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

(7) Overall risk of bias

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

Measures of treatment effect

Dichotomous data

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

Continuous data

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

Unit of analysis issues

Cluster-randomised trials

We would have included cluster-randomised trials in the analyses along with individually-randomised trials. We would have adjusted their sample sizes or standard errors using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we used ICCs from other sources, we would have reported this and conducted sensitivity analyses to investigate the effect of variation in the ICC. If we had identified both cluster-randomised trials and individually-randomised trials, we planed to synthesise the relevant information. We would have considered it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely.

We would have also acknowledged heterogeneity in the randomisation unit and performed a subgroup analysis to investigate the effects of the randomisation unit if necessary.

Cross-over trials were not considered in this review.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they had been allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

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

Assessment of reporting biases

When there were 10 or more studies in a meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually, and used formal tests for funnel plot asymmetry. We performed exploratory analyses to investigate any asymmetry we detected.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2011). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment

effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary when an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful we did not combine trials.

When we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

When we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful, and when it was, used random-effects analysis to produce it.

We carried out the following subgroup analysis by incorporating zinc status as subgroups as part of the primary comparison.

1. Risk of populations (population with no or low risk of zinc deficiency versus population with assumed risk of zinc deficiency).
2. Study settings (studies conducted in high income settings versus low income settings).

The primary outcomes were used in the subgroup analysis.

We assessed differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we assessed differences between subgroups by interaction tests.

Sensitivity analysis

We carried out sensitivity analysis to explore the effects of adequate allocation concealment, but found that restricting to only trials with adequate allocation concealment made very little difference to the results for the primary outcomes.

RESULTS

Description of studies

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

In this update we added three new randomised controlled trials (RCTs) to make a total of 20 included trials.

We included 20 RCTs involving over 15000 women and their babies. *See* table of Characteristics of included studies for details.

Participants and settings

Sixteen studies included women from low-income settings. One of the four studies in the higher-income or mixed-income settings only recruited women at risk of giving birth to small-for-gestational age babies (UK 1991a).

Baseline zinc concentrations and nutritional status

Women in most of the studies had, or were likely to have low zinc concentrations and low nutritional status. It is difficult to assess zinc status and most studies have assumed that pregnant women from low-income groups would be low in zinc as part of their overall poor nutritional status. Where studied, the improvement in serum zinc concentrations in the supplemented group supports this assumption (Bangladesh 2000; Peru 1999). The only studies likely to have included women with normal zinc concentrations were UK 1989; UK 1991a; UK 1991b.

Dosage of zinc supplementation

The dose of daily zinc supplementation ranged from 5 mg (China 2001) to 44 mg zinc per day (Denmark 1996). Some women in S Africa 1985 had doses of up to 90 mg zinc per day.

Duration of supplementation

Women were supplemented from before conception in Nepal 2003 with the shortest duration being from 26 completed weeks' gestation in some women in USA 1983; and USA 1985.

Types of interventions

Most trials (14/20) compared zinc with placebo (Bangladesh 2000; China 2001; Chile 2001; Denmark 1996; Ghana 2009; Iran 2010; Pakistan 2005; S Africa 1985; UK 1989; UK 1991a; USA 1983; USA 1985; USA 1989; USA 1995). In some trials (*see* Characteristics of included studies table); all women were also given iron, folate or vitamins or combinations of these. Three trials (Indonesia 1999; Indonesia 2001; Nepal 2003) had more than two arms, so these trials were analysed to compare women who received zinc with women who did not.

Nepal 2003 was a cluster-RCT - analyses adjusted for clustering were presented in study reports and so we did not need to perform additional calculations for these study results.

Adherence

Two studies (Chile 2001; Denmark 1996) excluded non-adhering women (85% and 60% compliance respectively) and the other 15 studies included or probably included non-adhering women in the analysis. Of the latter group, two studies (UK 1991a; USA 1983) presented at least some results separately for adhering women and

non-adhering women. Adherence was generally reported to be over 70%, except for Pakistan 2005; UK 1989; UK 1991a, where it was 50% to nearly 70%.

Excluded studies

We excluded 15 studies. *See* table of Characteristics of excluded studies for details.

Risk of bias in included studies

Risk of bias for included studies is summarised in Figure 1 and Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

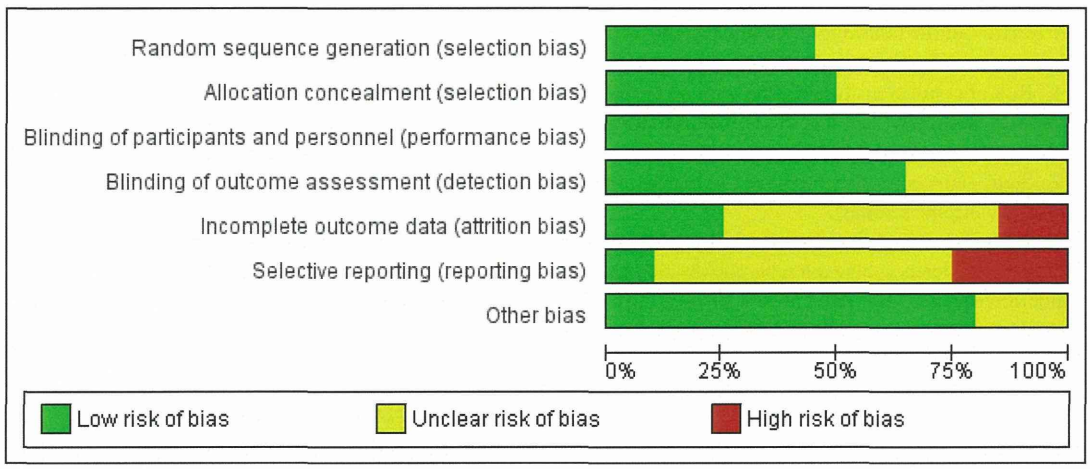

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.