Vitamin A supplementation during pregnancy (Review)

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ABSTRACT

Background
Vitamin A supplements have been recommended in pregnancy to improve outcomes that include maternal mortality and morbidity.

Objectives
To review the effectiveness of vitamin A supplementation during pregnancy, alone or in combination with other supplements, on maternal and newborn clinical and laboratory outcomes.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's specialised register of controlled trials (April 2002) and the Cochrane Controlled Trials Register (The Cochrane Library Issue 1, 2002).

Selection criteria
All randomised or quasi-randomised trials evaluating the effect of vitamin A supplementation in pregnant women. The types of intervention included vitamin A supplementation alone or in combination with other micro-nutrients.

Data collection and analysis
We assessed trials for methodological quality using the standard Cochrane criteria of adequacy of concealment. At least two reviewers independently assessed the trials for inclusion and extracted data. We collected information on blinding, loss to follow-up, setting, number of women, exclusion after randomisation and follow-up as well as supplementation type, dose and frequency. The outcomes we sought included maternal and neonatal clinical and laboratory outcomes.

Main results
Five trials involving 23,426 women were included. Because the trials were heterogeneous with regard to type of supplement given, duration of supplement use and outcomes measured, pooled results using meta analysis could not be performed. One large population based trial in Nepal showed a possible beneficial effect on maternal mortality after weekly vitamin A supplements. In this study a reduction was noted in all cause maternal mortality up to 12 weeks postpartum with Vitamin A supplementation (RR 0.60, 95% CI 0.37-0.97). Night-blindness was assessed in a nested case-control study within this trial and found to be reduced but not eliminated. Three trials examined the effect of vitamin A supplementation on haemoglobin levels. The trial from Indonesia showed a beneficial effect in women who were anaemic ([Hb] <11.0 g/dl). After supplementation, the proportion of women who became non-anaemic was 35% in the Vitamin A supplemented group, 68% in the iron-supplemented group, 97% in the group supplemented with both Vitamin A and iron and 16% in the placebo group. The two trials from Malawi did not corroborate these positive findings.

Authors' conclusions
Although the two trials from Nepal and Indonesia suggested beneficial effects of vitamin A supplementation, further trials are needed to determine whether vitamin A supplements can reduce maternal mortality and morbidity and by what mechanism.

PLAIN LANGUAGE SUMMARY

Vitamin A supplementation for pregnant women in areas where deficiency is common can reduce night-blindness, but more research is needed on other possible health benefits

Pregnant and breastfeeding women need extra vitamin A for themselves and their babies. Vitamin A deficiency can cause night-blindness, anaemia and other problems. It is very common in some areas in developing countries. While vitamin A can be increased by dietary changes, sometimes supplementation is the only option. Very high levels of supplementation can cause miscarriage and birth defects, but there is a safe daily dose. The review of trials found that daily or weekly vitamin A supplementation can reduce night-blindness in women living in high-risk areas. More research is needed to show if it has other benefits.

BACKGROUND

Vitamin A general:

Vitamin A, a fat soluble vitamin, is necessary for the maintenance and functioning of many body tissues especially for the growth and proliferation of epithelial cells. Vitamin A can be obtained from the diet in two forms: as preformed Vitamin A (retinal) and from some of the arotinoid pigments in food that can be cleaved in the body to give retinol. Preformed Vitamin A (usually in the form of retinyl esters) occurs naturally only in animals and the richest sources are liver, fish oils herring, sardines, tuna and dairy products (milk, cheese, butter, ice-cream). Between 25 and 35% of the dietary Vitamin A in the diet will come from carotenoids (usually beta-carotene) mainly from plant foods. Common sources of pro-vitamin carotenoids include carrots, yellow squash, dark leafy vegetables, corn, tomatoes, oranges, papayas and mangoes. The colour of fruits and vegetables is not necessarily an indication of its concentration of pro-Vitamin A. Tomatoes for example are rich in lycopene which is nutritionally inactive and the green colour of leafy vegetables is the result of chlorophyll which masks the yellow colour of the carotenoids.

Carotenoids can be converted to vitamin A in the liver where Vitamin A is stored. Absorption from plant sources is thought to be low and animal sources (i.e. including dairy products) may be needed to achieve adequate levels. Sufficient stores may be able to maintain a person's requirement for months. The digestion and absorption of vitamin A is closely associated with lipid absorption. Factors such as low dietary fat intake or intestinal infections may interfere with the absorption of vitamin A (Sivakumar 1972; Mahalanabis 1979).

Vitamin A plays a key role in the formation of rhodopsin, the visual pigment of the eye and is believed to be essential for normal embryogenesis, haematopoiesis, growth and epithelial differentiation.

Vitamin A in pregnancy and the new born:

In pregnancy, extra vitamin A is required for growth and tissue maintenance in the fetus, for providing it with some reserves and for maternal metabolism. Pregnant women have, according to WHO, a basal requirement of 370 mcg/d (microgram/day), which increases during lactation to 450 mcg/d (WHO 1995).

Retinol is teratogenic. A relationship has been suggested between the incidence of birth defects and high vitamin A intakes during pregnancy with an apparent threshold of near 10,000 international units (IU) per day (Mills 1997; Rothman 1995). Increased maternal levels of preformed vitamin A (retinoic acid) have been shown to be associated with spontaneous abortion and malformations involving the central nervous system and cardiac development (WHO 1998). A WHO expert group consultation concluded that daily doses of up to 10.000 IU (equivalent to 3000 mcg retinol) or weekly 25.000 IU after day 60 are probably safe especially in areas where vitamin A deficiency is thought to be common (WHO 1998).

During pregnancy, vitamin A is transferred to the fetus via the placenta by active mechanisms that maintain the transfer over a wide range of maternal dietary intake. In contrast, during lactation, vitamin A concentration in breast milk is more sensitive to variations in maternal intake (Ross 1994). The estimated requirements for vitamin A in newborn infants is 180 mcg/d with a safe intake level of 350 mcg/d.

Newborn infants normally have a low level of vitamin A in the liver and increase these stores in the first few months if the breast milk has adequate levels. Preterm infants have reduced hepatic (liver) stores and lower levels of retinol binding protein (the vitamin A carrier protein) in the plasma (Darlow 1998). Insufficient intake and reduced absorption by the immature gut may exacerbate the deficiency state in preterm infants.

Measurement of vitamin A status:

In the literature on Vitamin A authors have used a variety of different indicators and units of measurement. This can be confusing. In general the following conversions can be used:

- serum retinol 1 mcmol/l = 28.6 ug/dl or 10 mcg/dl = 100 mcg/l = 0.35 mcmol/l;

- for supplement doses 1 mcg retinol equivalent = 0.00349 mcmol retinol = 3.33 IU Vitamin A or, expressed differently, 1 IU Vitamin A = 0.3 mcg retinol and 0.00105 mcmol retinol.

There are problems associated with the biochemical assessment of vitamin A deficiency. Serum retinol, because of homeostatic control exerted by the liver, is not a good general indicator of vitamin A status. Despite these problems plasma retinol levels below 100 mcg/l are associated with low liver stores and an increase in clinical signs and symptoms of vitamin A deficiency. The WHO adopted the following interpretation of plasma levels (mcg/l) (WHO 1976): > 500 high, 200 to 500 normal, 100 to 200 low, < 100 deficient. When plasma levels are < 100 mcg/l (equivalent to 0.35 mcmol/l) in five per cent or more of the population, vitamin A deficiency must be considered a major public health problem.

As a result of normal physiological changes during pregnancy serum retinol levels have been shown to drop below non-pregnancy concentrations (Hytten 1991). Serum retinol concentrations of 1.05, 0.70 and 0.35 mcmol/l have ben used in the published literature to indicate inadequate, moderately inadequate and very inadequate liver stores respectively (Underwood 1990). It must be noted however that these 'cut-off' levels are largely taken from paediatric values and have not necessarily been evaluated in pregnancy. Dose response tests have recently been developed which can be used in the field to assess liver stores which may be a more accurate way of assessment of Vitamin A status (Underwood 1994; WHO 1994; Tanumidhardjo 1995).

It is thus not absolutely clear which cut-off points of serum retinol or dose response tests should be used in pregnancy as there are no studies of risk and morbidity in relation to different levels of vitamin A status. For many countries there are also still no accurate data on vitamin A status of pregnant women. However, in areas where night-blindness is common, vitamin A deficiency is often assumed to be widespread.

Vitamin A deficiency:

Vitamin A deficiency is thought to be common in many developing countries (WHO 1995). Much research has been devoted to child health but much less to maternal health. Reports of population deficiency are often based on the assessment of night-blindness and other eye symptoms among pre-school children in various countries. There is comparatively little published information on the occurrence of Vitamin A deficiency in pregnancy. In cases of marginal vitamin A sufficiency, the extra demands made by pregnancy could be expected to result in vitamin A deficiency symptoms in pregnant women. Estimates of the number of people affected or at risk of Vitamin A deficiency are approximations but it is thought that there is a significant problem in at least parts of most countries in Africa, South and South-East Asia and areas of Latin America and the Western Pacific (WHO 1995).

Most of the emphasis has been on effects of vitamin A deficiency on the eye. The most obvious deficiency signs are dryness of the conjunctiva and the cornea (xerophthalmia), which can lead to permanent eye damage. Another well known effect of vitamin A deficiency is night-blindness.

It is also known that a diet devoid of vitamin A results in decreased haemoglobin levels (Hodges 1978). Vitamin A deficiency has been found to co-exist with iron deficiency in a number of developing countries (Karyadi 1996). Several international studies have documented a positive association between serum retinol and haemoglobin concentration in children (Mejia 1977; Wolde-Gabriel 1993) and pregnant women (Suharno 1992). Anaemia in pregnancy has been associated with vitamin A deficiency (van den Broek 1998; van den Broek 2000).

The mechanism by which vitamin A supplementation can improve haemoglobin and iron status has not been elucidated. It has been suggested that vitamin A is required for the mobilisation and utilisation of iron for haemoglobin synthesis (Bloem 1990; Panth 1990; Mejia 1982). An anti infective role has also been proposed as infection is associated with decreased serum iron levels, suppressed erythropoiesis and lower haemoglobin concentration (Mejia 1988; Thurnham 1993).

Vitamin A is involved in the growth and differentiation of epithelial tissues and also has a role in immunoprotection (Thurnham 1989; Tomkins 1989). Infections most closely associated with vitamin A deficiency are those in which structure or function of the epithelium may be impaired such as measles, diarrhoea and respiratory disease. Febrile infections are associated with reduced serum levels of retinol binding protein and retinol. This is thought to be an acute phase reaction.
Finally, there is some evidence that dietary carotenoids have protective function against some human cancers (Rousseau 1992).

Vitamin A supplementation:

A number of studies have assessed the role of vitamin A supplementation on infectious mortality in children in developing countries. These have been systematically reviewed (Glasziou 1993). Vitamin A supplementation was associated with a 30% reduction of death with a larger reduction of 66% in children hospitalised with measles. Similar results were found in another review (Fawzi 1993).

Vitamin A supplementation together with iron has led to improved haemoglobin levels in a number of studies (Mejia 1988; Bloem 1990). Fortification of food stuffs with vitamin A in Guatemala (sugar) and Indonesia was reported to improve ferritin levels (Mejia 1982) and haemoglobin concentration (Muhilal 1988). Intervention studies in Indonesian girls showed that a multivitamin regimen including vitamin A together with iron supplementation was more effective than iron alone or a multivitamin without vitamin A for improving ferritin levels (Angeles-Agdeppa 1997).

Vitamin A supplementation in pregnancy:

Currently, WHO recommends routine vitamin A supplementation during pregnancy or at any time during lactation in areas

with endemic vitamin A deficiency (where night-blindness occurs) (WHO 1998). It is not clear whether this strategy has other beneficial effects such as reduction in maternal mortality, prevention of anaemia or infection or any harmful effects. It is therefore important to review the evidence regarding vitamin A supplementation during pregnancy before making any recommendation for practice.

OBJECTIVES

To review the effectiveness of vitamin A supplementation during pregnancy, alone or in combination with other supplements, on maternal and newborn clinical and laboratory outcomes.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised or quasi-randomised trials evaluating the effect of vitamin A supplementation in pregnant women. The outcome HIV transmission was not considered in this review.

Types of participants

Pregnant women receiving vitamin A supplementation either in areas with endemic vitamin A deficiency (inadequate intake) or in areas with presumed adequate intake.

Types of intervention

Vitamin A supplementation, alone or in combination with other supplements compared with control group. The control group could be placebo, no treatment or another intervention (for example iron).

Conversions:

Since researchers report vitamin A measurements in different units the following conversion figures could be useful: For serum retinol 10 mcg/dl = 0.35 mcmol/l, 20 mcg/dl = 0.70 mcmol/l and 30 mcg/dl = 1.05 mcmol/l. Similar for dose of supplement 1 mcg retinol equivalent = 1 mcg retinol l = 3.33 IU vitamin A.

Types of outcome measures

The outcomes of this review are maternal and perinatal clinical and laboratory outcomes. Vitamin A supplementation is tested for different but somewhat related outcomes such as maternal anaemia and maternal mortality as well as for reducing mother to child transmission of HIV. This review focuses on effects on maternal mortality and morbidity such as anaemia but not on HIV which is reviewed elsewhere.

The following outcomes are sought for this review:

Clinical:

1. maternal death;
2. anaemia;
3. night-blindness;
4. maternal sepsis (before delivery or in the postnatal period);
5. preterm birth (< 37 weeks);
6. low birth weight (< 2500 g);
7. neonatal infection;
8. perinatal mortality;
9. congenital malformations.

Laboratory:

1. haemoglobin level;
2. iron deficiency;
3. vitamin A deficiency;
4. maternal infection markers;
5. breast milk vitamin A content;
6. neonatal infection markers.

It is acknowledged that most of the outcomes listed above may be reported in different ways in terms of methods used or cut-offs chosen. Internationally recognized and acknowledged cut-offs (such as [Hb] < 11.0 g/dl for anaemia in pregnancy) are taken into account with all of the above.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

This review has drawn on the search strategy developed for the Pregnancy and Childbirth Group as a whole. The full list of journals and conference proceedings as well as the search strategies for the electronic databases, which are searched by the Group on behalf of its reviewers, are described in detail in the 'Search strategies for the identification of studies section' within the editorial information about the Cochrane Pregnancy and Childbirth Group. Briefly, the Group searches on a regular basis MEDLINE, the Cochrane Controlled Trials Register and reviews the Contents tables of a further 38 relevant journals received via ZETOC, an electronic current awareness service. Relevant trials, which are identified through the Group's search strategy, are entered into the Group's specialised register of controlled trials. Please see Review Group's details for more detailed information. Date of last search: April 2002.

In addition, the Cochrane Controlled Trials Register (The Cochrane Library, Issue 1, 2002) was searched using the terms: (vitamin* AND pregn*) OR (retino* AND pregn*).

METHODS OF THE REVIEW

Trials were assessed for methodological quality using the standard Cochrane criteria of adequacy of allocation concealment: adequate

(A), unclear (B), inadequate (C) or that allocation concealment was not used (D). Information on blinding of outcome assessment and loss to follow-up were also collected.

Inclusion and exclusion of identified trials and data extraction were conducted independently by two reviewers (R Kulier and AM Gülmezoglu or N van den Broek and AM Gülmezoglu). Number of losses to follow-up and post-randomisation exclusions were assessed systematically for each trial. Trials were excluded if there was an imbalance in groups, suggesting possibility of selection bias. A form was designed, both to facilitate the process of data extraction and to request additional (unpublished) information from the authors of the original reports. Any discrepancies between the reviewers in either the decision of inclusion or exclusion of studies or in data extraction, were resolved by discussion and requesting clarification from the authors of the original report if necessary. No discrepancies occurred in the current version of the review.

The following data were extracted:

Number of randomised women;
setting (country, hospital or population);
exclusion after randomisation and losses of follow-up;
method of randomisation and allocation concealment;
supplementation dose and frequency;
time of initiation of supplementation;
duration of supplementation;
pre-randomisation laboratory parameters of supplemented and control group (haemoglobin, vitamin A levels, iron status, inflammation markers) if available, and outcomes as listed in types of outcome measures.

Summary relative risks were calculated using a fixed effects model. If there was statistically significant or visual heterogeneity among trials, no summary estimates were to be used. Baseline intake of vitamin A in the population will be used as a stratification factor if there are adequate data (deficient versus adequate intake), as well as route of supplementation (oral/injectable) and masking of treatment.

There were no language preferences in the search or selection of the studies.

DESCRIPTION OF STUDIES

As of April 2002 four published and one unpublished randomised trials were identified.

There is one large trial from Nepal with several published papers (West 1999).

This trial was by far the largest with the inclusion of more than 20,000 deliveries. It was a cluster randomised field trial conducted in South-East Nepal in a total of 30 village development communities (VDC), which are small sub-districts, each of which comprises nine wards. A total of 270 wards were thus randomised to three groups of 90 each, including 44,646 women at reproductive age receiving a weekly single oral supplement of vitamin A (23 310 IU Vitamin A or 7000 mcg retinol equivalents) or beta-carotene (42 mcg, or 7000 mcg retinol equivalent) or placebo. Twenty two thousand one hundred and eighty nine pregnancies in 20,119 women occurred in a time period between April 1994 and September 1997. Pregnant women were eligible for the analysis if they had received supplements for at least five months before conception. Local field workers visited the women weekly at home and administered the supplements. The primary outcome of the trial was pregnancy related and direct mortality occurring until 12 weeks postpartum, including injury related deaths. Baseline characteristics such as age, arm circumference, diet or socioeconomic status were similar between the three groups. Compliance to trial medications was assessed biochemically and through interviews. The serum retinol (935 samples) and beta-carotene (916 samples) concentrations were measured at mid-pregnancy in a sub sample of women for assessment of compliance and respective levels for vitamin A and beta-carotene were raised in the supplemented (not placebo) groups implying consumption of the trial medications. Pregnant women were more likely to have received their supplements than women who did not become pregnant during the period of the trial. Over 75% of pregnant women received at least half their eligible doses of supplement but only half received 80% or more of the intended supplement.

In a later paper from this group the effect of Vitamin A and beta-carotene supplementation on fetal or early infant (less than six months) mortality was reported (Katz 2000). Fetal loss was defined as any reported miscarriage, stillbirth or maternal death during pregnancy. Pregnant women were interviewed from the time they declared themselves pregnant which was on average at four months gestation and three months later (i.e. at an average of seven months gestation). Women who delivered a live infant were followed and interviews were carried out at three months and six months post delivery to assess the health and survival of the infant and mother.

The same group set up a surveillance system to identify night-blindness in pregnant women (Christian 1998). They interviewed women in 19 of the 30 village development communities included in the vitamin A/beta carotene trial on a weekly basis about symptoms of night-blindness. Supplementation for women of reproductive age (as for the West trial above) had been started for approximately one year before pregnant women were enrolled into the night-blindness surveillance system in July 1994. All pregnancies reported by women in the area after this date for which an outcome was reported by June 1997 were included in the analysis by Christian et al (Christian 2000). During the course of the study 11,476 pregnancies were recruited in the night-blindness surveillance area. Each week women in the area were asked whether they were pregnant. No confirmatory test was used to validate their report. Once reported to be pregnant women were interviewed twice during pregnancy and twice during the six months after delivery to

obtain weekly histories of diet, health and work activity. Women who reported night-blindness for at least one week during pregnancy were considered night-blind cases. For women who were pregnant two or more times during the period of surveillance only details of the last pregnancy were considered. Survival status was recorded from the time women reported being pregnant until the end of the study which was September 1997 allowing at least 12 weeks after the outcome for all pregnancies. Mortality in women with and without night-blindness was compared in 877 women with night-blindness and 9545 women without night-blindness (Christian 1999) in a case control study design.

Ascertainment of cause of death was by the verbal autopsy method by interviewers masked to the supplementation group. Proximate causes of death were grouped into infection-related, obstetric, injury-related and miscellaneous causes.

One trial from Indonesia and two from Malawi aimed to reduce anaemia with vitamin A supplementation in pregnancy.

The trial conducted in Indonesia (Suharno 1993) included 305 women from 20 rural villages in West Java, 16 to 24 weeks pregnant with haemoglobin concentrations between 8.0 and 10.9 g/dl. Women were assigned to one of four groups to receive daily supplements: one group received Vitamin A (2.4 mg retinol as retinyl palmitate which equates to about 8000 IU Vitamin A) and placebo iron tablets, the second group received iron (60 mg elemental iron as ferrous sulphate) and placebo Vitamin A, the third group received both the Vitamin A and iron supplements (as described in groups one and two) and the fourth group received placebos only. Blood samples for haematologic parameters were taken before supplementation (which lasted two weeks) and two to seven days after the last supplements were given. The supplements were administered under the direct daily supervision of field workers.

The trial by Semba et al (Semba 2001) was conducted in women attending a teaching hospital antenatal clinic. Women were given daily supplements of either Vitamin A (3000 mcg retinol equivalent which equals 10 000 IU Vitamin A) or placebo. All women received daily iron (30 mg) and folate (400 mcg). In addition, all women received two doses of Fansidar during pregnancy as presumptive treatment for malaria. Outcomes were measured at 38 weeks and included haemoglobin concentration and erythropoietin. Iron status was measured using serum ferritin and markers of inflammation included C-reactive protein and alpha-acid glycoprotein. Vitamin A status was measured using serum retinol. Compliance with supplements was assessed via monthly tablet counts.

The van den Broek trial (van den Broek 2001) included a representative group of rural women attending antenatal clinic in southern Malawi. Women received daily supplements of either Vitamin 10 000 IU or Vitamin A 5000 IU or a placebo. In addition, all women received daily iron supplements (60 mg elemental iron as ferrous sulphate with 0.25 mg folic acid). All women also received presumptive malaria treatment at around 20 and 34 weeks' gestation consisting of three tablets of Fansidar (500 mg sulphadoxine with 25 mg pyrimethamine). Inclusion criteria included haemoglobin level < or = 11.0 g/dl and > 5.0 g/dl after determination of haemoglobin using the HemoCue screening method. Subsequent haemoglobin measurements were made using an automated (Coulter) counter. Thirty two per cent of women recruited were HIV positive. Mean duration of supplementation was 14 weeks. Gestational age at recruitment was not less than 12 weeks and not more than 24 weeks as assessed by ultrasonography. Blood samples were taken before supplementation was commenced and for up to two times during the antenatal period and two times postnatally. Only data related to the antenatal period is so far included in the review. Vitamin A status was determined using serum retinol as well as the modified relative dose response test (MRDR) (Tanumidhardjo 1995). Iron status was measured using serum ferritin and serum transferrin receptor levels. Measures of infection status included C-reactive protein (CRP), malaria and HIV status. Compliance was measured by two-weekly tablet counts and serum retinol measurements. The three main outcome measures were haemoglobin level, prevalence of anaemia ([Hb] < 11.0 g/dl) and severe anaemia ([Hb] < 8.0 g/dl) after supplementation. Secondary outcomes included vitamin A status, iron status and infection status.

There is one trial from the United Kingdom. Howells et al (Howells 1986) conducted a randomised trial among 29 Asian women living in the UK with plasma retinol concentrations < 1.24 µmol at 28 weeks gestation. The supplemented group received 8000 IU retinyl palmitate and 800 IU vitamin D daily, the control group received 1000 IU ergocalciferol (vitamin D) daily from week 30 until delivery. The outcome measures included maternal serum retinol level at term, cord blood retinol level and birthweight. It is not clear whether compliance was assessed during the study. It is not possible to determine the exact length of supplementation from their paper.

METHODOLOGICAL QUALITY

In the trial from Nepal (West 1999) there was no concealment of allocation due to the nature of the trial design. In this trial the clusters (wards or districts) were randomly allocated to one of three groups by drawing randomly numbered chits. This allocation was done centrally and the intervention was delivered to these districts on a weekly basis for the trial period (three years). All trial medications (capsules) were identical and the code was broken after all data collection and analysis were completed. However, if the capsules were opened the beta-carotene supplements were different in colour and consistency. No information is reported on whether unblinding occurred or not. The results were analysed, taking the cluster effect into account. Overall 157 women were lost to follow-up (70 in the vitamin A, 43 in the beta-carotene and 44 in the placebo group). A different mortality pattern in the lost

to follow-up group could change the significance of the results. The authors do not report on whether the population was stable or how the study handled women who might have emigrated from one village to another.

Mortality was evaluated on an intention to treat basis - by supplement assignment irrespective of compliance.

Pregnancy elated mortality was selected as the primary end-point rather than conventional maternal mortality which is limited to the first 42 days after delivery and excludes deaths due to injuries and accidents. Cause of death was established by obtaining a history of events and illnesses preceding death from family members of any woman who was known to have died. This was usually done within one month after the death had been reported. The information obtained from the family via interview was reviewed by two doctors (one an obstetrician -gynaecologist) who were blind to treatment allocation. In this way a 'proximate' cause of death was established (verbal autopsy). This method may be subject to considerable misclassification

In the Suharno trial from Indonesia (Suharno 1993), women were allocated sequential numbers and an independent researcher randomly labelled the medications red or blue (iron and placebo) and green or yellow (vitamin A and placebo). There is no information on the generation of randomisation sequence. It is reported that the code was broken after all analyses were completed.

In the Semba trial from Malawi (Semba 2001) treatment assignment was by using a computer random-number generator, treatment allocation was adequately concealed and supplements containing vitamin A folate and iron are described as being identical to those containing folate and iron only. There is no information about when the randomisation code was broken.

In the van den Broek trial from Malawi (van den Broek 2001) the randomisation schedules were prepared by statisticians not involved in the trial using a random generation procedure to assign treatments to each individual using consecutive numbers. Vitamin A and placebo were prepared in identical capsules and packaged in bottles containing supplies sufficient for 14 days. Women eligible for recruitment were allocated the next consecutive treatment number. The randomisation schedule was only broken after all data had been entered and checked with the exception of some CRP and serum retinol values. Analyses of these outstanding data were by laboratory technicians blinded to the treatment allocation.

In the UK trial (Howells 1986) there is no information about the method of randomisation and concealment. In addition, it is not clear whether the trial was blind and it would seem that the vitamin D supplement given with vitamin A differed from the vitamin D given to the group of women not receiving vitamin A.

RESULTS

The trials we identified were heterogeneous with regard to study design, with regard to interventions including the type, timing, dose and duration of treatment and with regard to the selected primary outcomes; therefore, a meta-analysis was not performed.

The main results of the largest trial from Nepal (West 1999) are listed in Table 01. This trial reported a reduction in all cause maternal mortality up to 12 weeks postpartum in the vitamin A and beta-carotene supplemented groups compared to the placebo group: relative risk (RR) 0.60 (95% confidence interval (CI) 0.37 to 0.97) in the vitamin A group and 0.51 (95% CI 0.30 to 0.86) in the beta-carotene group. Table 01 shows the deaths by supplementation group (Vitamin A, beta-carotene or placebo) classified by the authors as resulting from obstetric causes (including haemorrhage, eclampsia and other), infection (including gastroenteritis,sepsis, respiratory infection and other), deaths related to injury and deaths classified as miscellaneous. The impact of supplementation on cause related maternal mortality showed no statistically significant difference for obstetric or infectious causes between the groups. For miscellaneous causes, including chronic illnesses and uncertain causes, there were significantly less maternal deaths in the vitamin A group compared with the placebo group (RR 0.14, 95% CI 0.03 to 0.76).

Fetal or early infant survival was not found to be improved by supplementation. Fetal loss was reported to be 92.0 per 1000 pregnancies in the placebo group and this was comparable with the rates in the Vitamin A and beta-carotene supplemented groups. The relative risk (RR) of fetal loss was 1.06 (95% confidence interval (CI) 0.91 to 1.25) in the Vitamin A group and 1.03 (95% CI 0.87 to 1.19) in the group supplemented with beta-carotene when compared with the placebo group. Similarly there was no significant difference in mortality of live born babies at six months of age. The mortality rate to six months was 70.8 per 1000 live births in the placebo group with a relative risk of 1.05 (95% CI 0.87 to 1.25) in the Vitamin A group and 1.03 (95% CI 0.86 to 1.22) in the beta carotene supplemented group of women (Katz 2000) when compared with the placebo group.

Christian (Christian 1998) found night-blindness reduced in both, vitamin A and beta-carotene groups compared with the placebo group: RR 0.62, 95% CI 0.45 to 0.85 and RR 0.84, 95% CI 0.63 to 1.11, respectively, especially in women taking more than 96% of their supplements. This did not occur in women at a compliance level less than 40%, suggesting a dose response relationship.

The objective of the Suharno trial (Suharno 1993) was to evaluate the role of iron and vitamin A supplementation on treating anaemia during mid-pregnancy. The effect of the intervention was calculated by the increase in haemoglobin level in the treatment group minus the increase in the control group. Fifty four women (17%) were excluded from analyses due to loss to follow-up, non-

compliance or refusal to provide a blood sample. Mean standard deviation (SD) serum retinol at baseline was 1.08 (0.31) mcmol/l (n = 251). Prior to supplementation, the authors considered that no women were Vitamin A deficient (serum retinol levels < 0.35 mcmol/l) but 10% of women (25 of 251) had serum retinol concentrations between 0.35 and 0.70 µmol/l and could be considered to have marginal Vitamin A status. Supplementation with vitamin A increased mean serum retinol levels by 0.20 mcmol/l (0.12 to 0.28). The proportion of non-anaemic women was 35% in the vitamin A group, 68% in the iron group and 97% in the combined vitamin A and iron group. Vitamin A and iron given together resulted in a mean increase in haemoglobin concentration of 1.28 g/dl (95% CI 1.09 to 1.47). The authors calculate that one third of this was attributable to vitamin A (0.37 g/dl) and two thirds to iron (0.88 g/dl). Iron supplementation increased serum ferritin and decreased total iron binding capacity. These variables were not influenced by vitamin A supplementation.

The two trials conducted in Malawi did not show a similar effect of vitamin A on haemoglobin levels. In the Semba 2001 trial, a total of 66 women were lost to follow-up (32.5%). This included 30.3% in the vitamin A group and 35% in the control group. Loss to follow-up was because of missed visits, failure to have haemoglobin analysed and women moving out of the study area. There were no significant differences at baseline in haemoglobin, ferritin, C-reactive protein and plasma erythropoietin between the two groups. However, serum retinol was significantly lower in the vitamin A group compared with the control group. In the vitamin A group, 85.3% had serum retinol levels < 1.05 mcmol/l and 34.8% had levels < 0.70 mcmol/l. In the control group this was 70.9% and 24.7% respectively. Figures are not given for severely inadequate serum retinol (< 0.35 mcmol/l). Fifty per cent of women were anaemic ([Hb] < 11.0 g/dl) at entry into the trial. At 38 weeks gestation, 28.9% of women in the group receiving vitamin A and 35.2% in the control group were anaemic ([Hb] < 11.0 g/dl) (p = 0.46 by chi-square). Mean (standard error of mean) change in haemoglobin was 0.47 (0.16) g/dl in the vitamin A group (n = 63) and 0.73 (0.23) g/dl in the control group (n = 52). Mean haemoglobin concentrations were not significantly different between the vitamin A and control group at 38 weeks even after adjustment for baseline vitamin A deficiency, iron deficiency anaemia and elevated acute phase proteins. Similarly, there were no differences in mean plasma erythropoietin concentration between the groups.

In the van den Broek 2001 trial, of the 700 women who were randomised, a repeat blood sample to assess the effect of the intervention was not available for 77 women (distributed evenly between the three groups) and a further 93 women were lost to follow-up prior to delivery assessment. Reasons for dropping out of the study included maternal death (two), pregnancy loss or premature delivery (72), declined to give further blood sample (68) and moved from the area. At baseline there were no significant differences between women in the three groups with regard to gestational age, indices of vitamin A status, iron and infective status. There was no difference in length of supplementation between the groups. After supplementation the mean (SD) (mcmol/l) change in serum retinol did not differ between treatment groups; -0.03 (0.75) mcmol/l for the placebo group, 0.02(0.64) mcmol/l for the group receiving 5000 IU vitamin A and 0.06 (0.65) mcmol/l for the group receiving 10,000 IU vitamin A per day. Women who started with adequate vitamin A stores in the liver (as measured by MRDR) were more likely to have inadequate stores at the end of pregnancy if they had been given placebo rather than vitamin A supplements.

The prevalence of any anaemia ([Hb] < 11.0 g/dl) or severe anaemia ([Hb] < 8.0 g/dl) was not significantly influenced by vitamin A supplementation (overall comparison of the three groups. A mean increase in haemoglobin concentration of 1.0 g/dl was noted in anaemic women and a mean increase of 2.5 g/dl in women with severe anaemia. There was no effect of vitamin A on iron status or markers of infection. The study group also included 122 women who were not anaemic at entry into the trial. In the tables of comparison, data are given for anaemic women ([Hb] < 11.0 g/dl). Vitamin A 5000 IU and 10,000 IU are pooled together except for comparison of high dose and low dose vitamin A.

In the Howells 1986 trial, all women were followed to delivery. Mean serum retinol concentration was noted to be lower in Asian women than in non-Asian women who had been matched for age parity and socio-economic background. Women were selected to enter this trial if their serum retinol was < 1.24 mcmol/l (= 35.5 mcg/dl) as measured at 28 weeks' gestation. Mean (SD) serum retinol prior to supplementation was 1.03 (0.15) mcmol/l for the control group and 1.10 (0.23) mcmol/l for the group to receive vitamin A. Mean serum retinol can be considered to have been inadequate. Haemoglobin levels are not reported. Mean serum retinol in women who received 8000 IU vitamin A in addition to 800 IU vitamin D was higher than serum retinol in the group who had received 1000 IU vitamin D but no vitamin A (mean (SD) serum retinol 1.32 (0.36) mcmol/l and 1.00 (0.28) mcmol/l t = 2.31, p < 0.03). Cord blood retinol was also higher in the group receiving vitamin A but this did not reach statistical significance. There was no difference in mean birthweight or anthropometric measurements in the neonates.

DISCUSSION

The trial conducted in South-East Nepal from 1994 to 1997 has generated most interest and controversy regarding the role of vitamin A supplementation during pregnancy. This trial was carefully planned and executed as a large cluster randomised trial. However, several controversies need to be addressed.

The authors explicitly state that the primary outcome of the intervention was reduction in pregnancy related mortality up to 12

weeks postpartum including injuries. Although the appropriateness of this selection could be questioned the authors provided the data with regard to the conventional definition of maternal mortality (up to six weeks postpartum, excluding injuries) and for specific causes of deaths.

They report a substantial reduction in mortality for all cases in the supplementation groups (40% reduction in the vitamin A group and 50% in the beta-carotene group). The specific causes of deaths are summarised in Table 01. The fact that most of the mortality contributing to the difference between placebo and supplemented groups occurred in injury, chronic illness and uncertain cause of death categories raises the question of biological plausibility. It is difficult to find a biological explanation (except for improved vision leading to fewer injuries) to the reduction in injury related deaths. However, if real, this is potentially an important intervention to improve maternal health.

The authors state that since the mortality rates were similar between vitamin A and beta-carotene, and beta-carotene is the provitamin A, they combined the two groups which results in a combined effect of 44% reduction in pregnancy-related deaths up to 12 weeks postpartum. However, beta-carotene possesses antioxidant properties which may have implications for pregnancy specific morbidities such as pre-eclampsia/eclampsia. Since vitamin A does not possess antioxidant properties pooling of the two groups might not be biologically appropriate.

It is not clear to what extent losses to follow-up (157 women) and the possibility of unblinding by opening the capsules could distort the results (Olsen 1999). Regardless, the trial is important in that it provides data on a large-scale population-based intervention which seems to be promising. These results indicate the need for further research to provide more conclusive answers, and if positive, more information on the feasibility and cost-effectiveness of these two interventions (vitamin A and beta-carotene).

The same group has published several other reports from the same study in nested case-control designs. The results indicate a reduction in night-blindness with vitamin A supplementation which is expected. However, secondary, non-randomised group analyses should be viewed with caution in general.

The trials by Suharno 1993, Semba 2001 and van den Broek 2001 are smaller in size and address different questions. Serum retinol levels were increased with supplementation in all trials. The Suharno 1993 trial suggests that vitamin A and iron combination may be more effective than either iron or vitamin A alone in treating mild anaemia in mid-pregnancy. The outcome assessment was done immediately following supplementation for eight weeks and non-compliant women were excluded from the analysis. Compliance was very closely monitored.

The two trials from Malawi (Semba 2001; van den Broek 2001) are similar to the Suharno 1993 trial in that the objective was to treat anaemia. Instead of the factorial design of the Suharno 1993 trial, the Malawi trials used vitamin supplements in a population receiving iron and folic acid supplementation as part of routine recommended antenatal care. The results of the Malawi trials do not corroborate the favourable findings of the trial conducted in Indonesia (Suharno 1993). There may be several reasons for this discrepancy. The van den Broek 2001 and Semba 2001 trials were conducted in an area with endemic malaria and where night-blindness is not commonly noticed within the population. In contrast, the studies in Indonesia (Suharno 1993) and Nepal (West 1999) were conducted in settings where night-blindness is reported to be common.

Even though serum retinol is not a good marker of vitamin A status, it was used in all three studies. In the Suharno 1993 trial, 10% of women had marginal vitamin A status (serum retinol 0.35-0.70 mcmol/l). In the Semba 2001 trial, between 25% and 35% of women were reported to have marginal levels of serum retinol and in the van den Broek 2001 trial 8.6% had serum retinol levels below 0.70 mcmol/l. Dose response tests are better markers of vitamin A status and, although more cumbersome, their use in future studies must be encouraged.

It has been suggested that vitamin A supplementation, especially in the postpartum period, will reduce the incidence of sepsis. In the trials reviewed, markers of inflammation were assessed but vitamin A was not found to have a significant effect on these. We have no data on outcomes such as sepsis. Even with effects on anaemia there are no data to support that women would be better off at delivery or immediate postpartum period if they were supplemented with vitamin A.

There are no reports of side-effects or adverse events in the trials published so far.

We are aware of vitamin A supplementation trials which have been either completed or currently recruiting. These trials will help to increase the evidence base with regard to the role of vitamin A supplementation in improving maternal outcomes. A trial conducted in Indonesia looking at infection and anaemia with vitamin A and zinc supplementation has also been completed and expected to be reported in the near future (Hakimi 1999). We hope that these and other trials will assist in policy making regarding the role of vitamin A supplementation during pregnancy in the near future.

AUTHORS' CONCLUSIONS

Implications for practice

Night-blindness is a condition that occurs as a consequence of inadequate vitamin A intake. Therefore, in settings where it is not feasible to increase vitamin A intake through dietary means and where night-blindness is endemic, vitamin A supplementation should be implemented. However, the evidence reviewed here is not strong enough to justify antenatal vitamin A supplementation

in these settings as a strategy to reduce adverse maternal outcomes such as anaemia, sepsis and death.

Implications for research

The findings of the Nepal trial are encouraging to conduct more research in this area. The main question that needs to be addressed is whether vitamin A supplementation reduces maternal mortality and morbidity. Further evidence on biologically plausible mechanisms of morbidity reduction such as reduced incidence of sepsis and/or reduced markers of inflammation are needed in this respect. Also, further evidence on the effectiveness of adding vitamin A to iron and folic acid for treatment of anaemia is needed. None of the trials have adequately addressed the side-effects and potential adverse events from vitamin A supplementation and this aspect deserves more attention if vitamin A supplementation is to be implemented in large-scale programmes.

It was noted that there was a difference between the trials with regard to the dose of vitamin A given, the combination with additional micronutrients (iron, folate, vitamin D) and the duration of supplementation. Also cut off points and methods used for the assessment of vitamin A status were dissimilar and comparisons therefore difficult to make.

POTENTIAL CONFLICT OF INTEREST

N van den Broek is involved in one of the included studies, the data for which was extracted by other members of the review team.

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TABLES

Characteristics of included studies

Study	**Howells 1986**
Methods	Randomised. No further details provided.
Participants	Asian women attending antenatal clinic in London who had serum retinol levels < 1.24 umol/l at 28 weeks gestation.
Interventions	Vitamin A 8000 IU as retinyl palmitate with 800 IU Vitamin D daily versus 1000 IU Vitamin D. All supplements given daily. Duration of supplementation was about 8 weeks or more.
Outcomes	Maternal serum retinol and cord blood serum retinol at term as well as neonatal outcomes such as birthweight.
Notes	
Allocation concealment	B – Unclear

Study	**Semba 2001**
Methods	Randomised, double blind, placebo controlled trial.
Participants	HIV negative women attending antenatal clinic at an urban hospital.

Characteristics of included studies (*Continued*)

Interventions	Vitamin A 3000 ug equivalent iron (30 mg) and folate (400 ug) versus iron (30 mg) and folate (400 ug). All supplements given daily. Duration of supplementation was for 10 weeks or more. All women received presumptive treatment for malaria and sexually transmitted disease.
Outcomes	Haemoglobin and erythropoietin levels at 38 weeks gestation.
Notes	32.5% of women were lost to follow-up as a result of missed study visit (42), [Hb] not analysed (9) and moved out of the area (15).
Allocation concealment	A – Adequate

Study	**Suharno 1993**
Methods	Randomised, double-blind, placebo-controlled. The preparations were labelled in different colours for active and placebos by an independent researcher and given to patients following a sequential list of 1 to 100. Iron and vitamin A active and placebos were supplied by two pharmaceutical companies. It is not mentioned in the report if active and placebos were identical.
Participants	305 women at 16-24 weeks pregnancy, Haemoglobin 80-109 g/l, living in 20 rural villages in West Java, Indonesia.
Interventions	Vitamin A: 2, 4 mg retinol; ferrous sulphate: 60 mg/day; vitamin A + ferrous sulphate combination in same doses; placebo. The treatments were continued on a daily basis for 8 weeks.
Outcomes	Anaemia following treatment.
Notes	54 women were excluded after randomization (17.7%) for the following reasons: changed location (11), took supplements for < 8 weeks (23), refused to provide blood sample (10), not available to provide a second blood sample (10).
Allocation concealment	C – Inadequate

Study	**West 1999**
Methods	Randomised, double-blind, placebo controlled trial. Cluster randomised: 30 villages with 9 wards each were randomised to study the effect of retinol equivalent's supplementation on infant and maternal mortality. In 171 of the wards were surveilled regarding the incidence of night-blindness and the effect of vitamin a and beta carotene. Pregnant women were asked weekly about symptoms of night-blindness.
Participants	9932 women in their first pregnancies were included. Inclusion criteria: minimum of 4 weeks pregnancy, questioned about nightblindness for =/> 1 week, survival of the pregnancy.
Interventions	Vitamin A: 23,300 IU as retinyl palmitate (7,000 retinol equivalents); ß-carotene: 42 mg of all trans form (7,000 retinol equivalents); Placebo: identical placebos. Tablets were opaque, gelatinous and contained peanut oil, distributed on a weekly basis. All above doses are weekly doses.
Outcomes	Night blindness.
Notes	
Allocation concealment	D – Not used

Study	**van den Broek 2001**
Methods	Randomised double blind placebo controlled. Active and placebo preparations were identical.
Participants	700 women attending antenatal clinic in rural southern Malawi. Median screening [Hb] at entry into trial 9.4 g/dl with 15.3% of women severely anaemic. ([Hb] < 8.0 g/dl).

Interventions	Vitamin A 10,000 IU daily or 5000 IU daily or placebo in identical tablets. All women received iron supplements (60 mg elemental iron with 0.25 mg folic acid). All women received presumptive treatment for malaria on two occasions. Mean duration of treatment was 13.7 weeks for anaemic women and 12.9 weeks for women with severe anaemia.
Outcomes	Anaemia following treatment. Iron status as measured by serum ferritin and serum transferrin receptor. Vitamin A status as measured by serum retinol and the modified relative dose response test. Infective status as measured by CRP, malaria parasitaemia and HIV status.
Notes	77 women dropped out before 28 weeks gestation (1 maternal death, 26 pregnancy loss,11 moved from the area and 39 women declined to continue the study. Of the 623 women who continued the trial there were 530 who were assessed a second time at 36-38 weeks gestation. (1 further maternal death, 4 pregnancy loss, 42 premature delivery, 10 missed appointments, 7 moved from area and 29 declined to continue).
Allocation concealment	A – Adequate

CRP = C-reactive protein
IU = international unit

Characteristics of excluded studies

Study	Reason for exclusion
Chawla 1995	Not a randomised controlled trial.
Panth 1990	Not a randomised controlled trial.
Sivakumar 1997	Not a randomised controlled trial.

ADDITIONAL TABLES

Table 01. Deaths in the West 1999 trial

Cause	Vitamin A	ß-carotene	Placebo
Obstetric			
Total	17/7747	10/7201	18/7241
Mortality/100,000 pregnancies	219	139	249
Relative risk (95% CI)	0.88 (0.42;1.81)	0.56 (0.24;1.31)	1.00
Infection			
Total	15/7747	9/7201	15/7241
Mortality/100,000 pregnancies	194	125	207
Relative risk (95% CI)	0.94 (0.42;2.05)	0.60 (0.24;1.51)	1.00
Related to injury			
Total	0/7747	1/7201	5/7241
Mortality/100,000 pregnancies	0	14	69
Relative risk (95% CI)	0	0.20 (0.02;2.32)	1.00
Miscellaneous			

Table 01. Deaths in the West 1999 trial (*Continued*)

Cause	Vitamin A	ß-carotene	Placebo
Total	2/7747	5/7201	13/7241
Mortality/100,000 pregnancies	26	69	180
Relative risk (95% CI)	0.14 (0.03;0.76)	0.38 (0.13;1.21)	1.00

ANALYSES

Comparison 01. Vitamin A versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 serum retinol mcmol/l	1	125	Weighted Mean Difference (Fixed) 95% CI	0.15 [0.04, 0.26]
02 anaemia	1	125	Relative Risk (Fixed) 95% CI	0.78 [0.63, 0.96]
03 haemoglobin concentration g/dl	1	125	Weighted Mean Difference (Fixed) 95% CI	0.40 [0.22, 0.58]
04 change in haemoglobin (g/dl)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable

Comparison 02. Vitamin A versus other micronutrient

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 serum retinol mcmol/l	1	126	Weighted Mean Difference (Fixed) 95% CI	0.15 [0.04, 0.26]
02 anaemia	1	126	Relative Risk (Fixed) 95% CI	2.05 [1.37, 3.07]
03 haemoglobin concentration g/dl	1	126	Weighted Mean Difference (Fixed) 95% CI	-0.40 [-0.58, -0.22]

Comparison 03. Vitamin A - High dose versus low dose

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 serum retinol (mcmol/l)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
02 anaemia	1	387	Relative Risk (Fixed) 95% CI	1.01 [0.87, 1.16]

Comparison 04. Vitamin A as part of a multimicronutrient supplement versus micronutrient

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 serum retinol mcmol/l	2	155	Weighted Mean Difference (Fixed) 95% CI	0.17 [0.06, 0.28]
02 anaemia	3	813	Relative Risk (Fixed) 95% CI	0.91 [0.80, 1.04]
03 haemoglobin concentration g/dl	1	126	Weighted Mean Difference (Fixed) 95% CI	0.50 [0.31, 0.69]
04 change in haemoglobin concentration (g/dl)	1	115	Weighted Mean Difference (Fixed) 95% CI	-0.26 [-0.33, -0.19]

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; *Pregnancy Outcome; Randomized Controlled Trials; Vitamin A [*administration & dosage]

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Vitamin A supplementation during pregnancy
Authors	van den Broek N, Kulier R, Gülmezoglu AM, Villar J
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Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Vitamin A versus placebo, Outcome 01 serum retinol mcmol/l

Review: Vitamin A supplementation during pregnancy

Comparison: 01 Vitamin A versus placebo

Outcome: 01 serum retinol mcmol/l

Study	Vitamin A		placebo		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Suharno 1993	63	1.25 (0.30)	62	1.10 (0.33)		100.0	0.15 [0.04, 0.26]
Total (95% CI)	63		62			100.0	0.15 [0.04, 0.26]
Test for heterogeneity: not applicable							
Test for overall effect z=2.66 p=0.008							

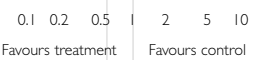
Analysis 01.02. Comparison 01 Vitamin A versus placebo, Outcome 02 anaemia

Review: Vitamin A supplementation during pregnancy

Comparison: 01 Vitamin A versus placebo

Outcome: 02 anaemia

Study	Vitamin A	placebo	Relative Risk (Fixed)	Weight	Relative Risk (Fixed)
	n/N	n/N	95% CI	(%)	95% CI
01 [Hb] < or = 11.0 g/dl (number of women)					
Suharno 1993	41/63	52/62		100.0	0.78 [0.63, 0.96]
Subtotal (95% CI)	63	62		100.0	0.78 [0.63, 0.96]
Total events: 41 (Vitamin A), 52 (placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.35 p=0.02					
02 [Hb] < 8.0 g/dl (number of women)					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Vitamin A), 0 (placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	63	62		100.0	0.78 [0.63, 0.96]
Total events: 41 (Vitamin A), 52 (placebo)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.35 p=0.02					



Analysis 01.03. Comparison 01 Vitamin A versus placebo, Outcome 03 haemoglobin concentration g/dl

Review: Vitamin A supplementation during pregnancy

Comparison: 01 Vitamin A versus placebo

Outcome: 03 haemoglobin concentration g/dl

Study	Vitamin A N	Vitamin A Mean(SD)	placebo N	placebo Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Suharno 1993	63	10.90 (0.50)	62	10.50 (0.51)		100.0	0.40 [0.22, 0.58]
Total (95% CI)	63		62			100.0	0.40 [0.22, 0.58]
Test for heterogeneity: not applicable							
Test for overall effect z=4.43 p<0.00001							

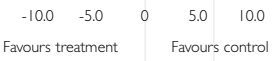
Analysis 01.04. Comparison 01 Vitamin A versus placebo, Outcome 04 change in haemoglobin (g/dl)

Review: Vitamin A supplementation during pregnancy

Comparison: 01 Vitamin A versus placebo

Outcome: 04 change in haemoglobin (g/dl)

Study	Vitamin A N Mean(SD)	placebo N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



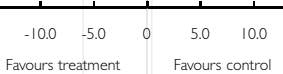
Analysis 02.01. Comparison 02 Vitamin A versus other micronutrient, Outcome 01 serum retinol mcmol/l

Review: Vitamin A supplementation during pregnancy

Comparison: 02 Vitamin A versus other micronutrient

Outcome: 01 serum retinol mcmol/l

Study	Vitamin A N	Vitamin A Mean(SD)	micronutrient N	micronutrient Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Suharno 1993	63	1.25 (0.30)	63	1.10 (0.32)		100.0	0.15 [0.04, 0.26]
Total (95% CI)	63		63			100.0	0.15 [0.04, 0.26]
Test for heterogeneity: not applicable							
Test for overall effect z=2.71 p=0.007							



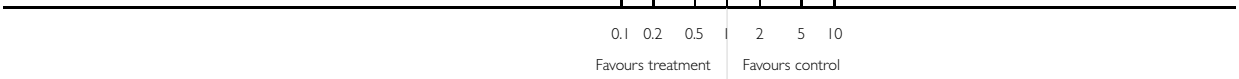
Analysis 02.02. Comparison 02 Vitamin A versus other micronutrient, Outcome 02 anaemia

Review: Vitamin A supplementation during pregnancy

Comparison: 02 Vitamin A versus other micronutrient

Outcome: 02 anaemia

Study	Vitamin A n/N	micronutrient n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 [Hb] < or = 11.0 g/dl (number of women)					
Suharno 1993	41/63	20/63		100.0	2.05 [1.37, 3.07]
Subtotal (95% CI)	63	63		100.0	2.05 [1.37, 3.07]
Total events: 41 (Vitamin A), 20 (micronutrient)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.48 p=0.0005					
02 [Hb] < 8.0 g/dl (number of women)					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Vitamin A), 0 (micronutrient)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	63	63		100.0	2.05 [1.37, 3.07]
Total events: 41 (Vitamin A), 20 (micronutrient)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.48 p=0.0005					



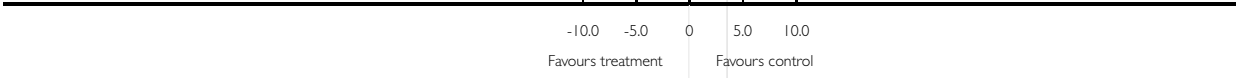
Analysis 02.03. Comparison 02 Vitamin A versus other micronutrient, Outcome 03 haemoglobin concentration g/dl

Review: Vitamin A supplementation during pregnancy

Comparison: 02 Vitamin A versus other micronutrient

Outcome: 03 haemoglobin concentration g/dl

Study	Vitamin A N	Vitamin A Mean(SD)	micronutrient N	micronutrient Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Suharno 1993	63	10.90 (0.50)	63	11.30 (0.52)		100.0	-0.40 [-0.58, -0.22]
Total (95% CI)	63		63			100.0	-0.40 [-0.58, -0.22]
Test for heterogeneity: not applicable							
Test for overall effect z=4.40 p=0.00001							



Analysis 03.01. Comparison 03 Vitamin A - High dose versus low dose, Outcome 01 serum retinol (mcmol/l)

Review: Vitamin A supplementation during pregnancy

Comparison: 03 Vitamin A - High dose versus low dose

Outcome: 01 serum retinol (mcmol/l)

Study	high dose Vit A N Mean(SD)	low dose Vit A N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

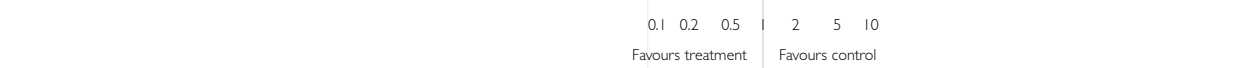
Analysis 03.02. Comparison 03 Vitamin A - High dose versus low dose, Outcome 02 anaemia

Review: Vitamin A supplementation during pregnancy

Comparison: 03 Vitamin A - High dose versus low dose

Outcome: 02 anaemia

Study	high dose Vit A n/N	low dose Vit A n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 [Hb] < or = 11.0 g/dl (number of women)					
van den Broek 2001	127/193	127/194		100.0	1.01 [0.87, 1.16]
Subtotal (95% CI)	193	194		100.0	1.01 [0.87, 1.16]
Total events: 127 (high dose Vit A), 127 (low dose Vit A)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.07 p=0.9					
02 [Hb] < 8.0 g/dl (number of women)					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (high dose Vit A), 0 (low dose Vit A)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	193	194		100.0	1.01 [0.87, 1.16]
Total events: 127 (high dose Vit A), 127 (low dose Vit A)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.07 p=0.9					



Analysis 04.01. Comparison 04 Vitamin A as part of a multimicronutrient supplement versus micronutrient, Outcome 01 serum retinol mcmol/l

Review: Vitamin A supplementation during pregnancy

Comparison: 04 Vitamin A as part of a multimicronutrient supplement versus micronutrient

Outcome: 01 serum retinol mcmol/l

Study	Vit A+ micronutrient		micronutrient		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Howells 1986	14	1.32 (3.60)	15	1.00 (0.28)		0.3	0.32 [-1.57, 2.21]
Suharno 1993	63	1.27 (0.30)	63	1.10 (0.32)		99.7	0.17 [0.06, 0.28]
Total (95% CI)	77		78			100.0	0.17 [0.06, 0.28]

Test for heterogeneity chi-square=0.02 df=1 p=0.88 I^2 =0.0%

Test for overall effect z=3.09 p=0.002

Analysis 04.02. Comparison 04 Vitamin A as part of a multimicronutrient supplement versus micronutrient, Outcome 02 anaemia

Review: Vitamin A supplementation during pregnancy

Comparison: 04 Vitamin A as part of a multimicronutrient supplement versus micronutrient

Outcome: 02 anaemia

Study	Vit A+ micronutrient	micronutrient	Relative Risk (Fixed)	Weight	Relative Risk (Fixed)
	n/N	n/N	95% CI	(%)	95% CI
01 [Hb] < or = 11.0 g/dl (number of women)					
Semba 2001	18/63	18/52		9.8	0.83 [0.48, 1.42]
Suharno 1993	2/63	20/63		10.0	0.10 [0.02, 0.41]
van den Broek 2001	254/387	119/185		80.2	1.02 [0.90, 1.16]
Subtotal (95% CI)	513	300		100.0	0.91 [0.80, 1.04]
Total events: 274 (Vit A+ micronutrient), 157 (micronutrient)					
Test for heterogeneity chi-square=12.57 df=2 p=0.002 I^2 =84.1%					
Test for overall effect z=1.43 p=0.2					
02 [Hb] < 8.0 g/dl (number of women)					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Vit A+ micronutrient), 0 (micronutrient)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	513	300		100.0	0.91 [0.80, 1.04]
Total events: 274 (Vit A+ micronutrient), 157 (micronutrient)					
Test for heterogeneity chi-square=12.57 df=2 p=0.002 I^2 =84.1%					
Test for overall effect z=1.43 p=0.2					

Analysis 04.03. Comparison 04 Vitamin A as part of a multimicronutrient supplement versus micronutrient, Outcome 03 haemoglobin concentration g/dl

Review: Vitamin A supplementation during pregnancy

Comparison: 04 Vitamin A as part of a multimicronutrient supplement versus micronutrient

Outcome: 03 haemoglobin concentration g/dl

Study	Vit A+micronutrient		micronutrient		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Suharno 1993	63	11.80 (0.55)	63	11.30 (0.52)		100.0	0.50 [0.31, 0.69]
Total (95% CI)	63		63			100.0	0.50 [0.31, 0.69]
Test for heterogeneity: not applicable							
Test for overall effect z=5.24 p<0.00001							

Analysis 04.04. Comparison 04 Vitamin A as part of a multimicronutrient supplement versus micronutrient, Outcome 04 change in haemoglobin concentration (g/dl)

Review: Vitamin A supplementation during pregnancy

Comparison: 04 Vitamin A as part of a multimicronutrient supplement versus micronutrient

Outcome: 04 change in haemoglobin concentration (g/dl)

Study	VitA+micronutrient		micronutrient		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Semba 2001	63	0.47 (0.16)	52	0.73 (0.23)		100.0	-0.26 [-0.33, -0.19]
Total (95% CI)	63		52			100.0	-0.26 [-0.33, -0.19]
Test for heterogeneity: not applicable							
Test for overall effect z=6.89 p<0.00001