Vitamin A and Carotenoids During Pregnancy and Maternal, Neonatal and Infant Health Outcomes: a Systematic Review and Meta-Analysis

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Vitamin A and carotenoids during pregnancy and maternal, neonatal and infant health outcomes: A systematic review and meta-analysis

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Summary

Vitamin A (VA) deficiency during pregnancy is common in low income countries and a growing number of intervention trials have examined the effects of supplementation during pregnancy on maternal, perinatal, and infant health outcomes.

We systematically reviewed the literature to identify trials isolating the effects of VA or carotenoid supplementation during pregnancy on maternal, fetal, neonatal and early infant health outcomes. Meta-analysis was used to pool effect estimates for outcomes with more than one comparable study. We used GRADE criteria to assess the quality of individual studies and the level of evidence available for each outcome.

We identified 23 eligible trials of which 17 had suitable quality for inclusion in meta-analyses. VA or beta-carotene (C) supplementation during pregnancy did not have a significant overall effect on birthweight indicators, preterm birth, stillbirth, miscarriage, or fetal loss. Among HIV-positive women, supplementation was protective against low birthweight (<2.5 kg), RR=0.79, [95% CI 0.64, 0.99], but no significant effects on preterm delivery or small-for-gestational age were observed. Pooled analysis of the results of three large randomized trials found no effects of VA supplementation on neonatal/infant mortality, or pregnancy-related maternal mortality, random effects RR=0.86, [0.60, 1.24] although high heterogeneity was observed in the maternal mortality estimate[I^2=74%, p=0.02]. VA supplementation during pregnancy was found to improve hemoglobin levels and reduce anemia risk (<11.0 g/dL) during pregnancy random effects RR=0.81 [0.69, 0.94], also with high heterogeneity (I^2=52%, p=0.04). We found no effect of VA/ C supplementation on mother-to-child HIV transmission in pooled analysis, although some evidence suggests that it may increase transmission.

There is little consistent evidence of benefit of maternal supplementation with VA or C during pregnancy on maternal or infant mortality. While there may be beneficial effects for certain outcomes, there may also be potential for harm through increased HIV transmission in some populations.

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Introduction

It has been estimated that about 19 million pregnant women in low income countries each year are affected by vitamin A (VA) deficiency, the majority in South and Southeast Asia.[1, 2] Nearly 10 million women suffer from night blindness during pregnancy, a condition often caused by VA deficiency and associated with a constellation of adverse health and nutritional conditions among mothers and infants.[1, 3–5]

Dietary VA is found as preformed retinol in animal sources (such as liver, eggs, and milk), as retinyl esters in fortified foods, and as provitamin A carotenoids found in green leafy vegetables and yellow/orange fruits such as mangos and papaya.[6] Although many provitamin A carotenoids have been identified, -Carotene (-C) has the highest conversion rates to retinol and additionally has anti-oxidative properties. Lycopene is a carotenoid without provitamin A activity but is an efficient anti-oxidant.

The recommended safe intake of VA during pregnancy by FAO/WHO is 800 μg RE/day (2664 IU)[7]. VA is known to have teratogenic effects if consumed at high doses during early pregnancy, and the FAO/WHO advise limiting intake to a maximum of 3000μg retinol equivalents (RE) per day (10,000 IU) or weekly intakes of 25,000 IU to minimize risks.[7] One approach used in some trials to try to meet the needs of highly deficient populations while minimizing risks of teratogenicity has been to include both VA and -C in supplements.[8, 9]

VA deficiency is most often considered to be a problem of public health concern among preschool age children (age 6–59 months) as it increases risk of mortality from infectious disease, particularly measles, diarrhea, and malaria.[6, 10] Findings that high dose supplementation with VA two to three times per year reduces the risk of all cause child mortality by an average of 24% form a solid evidence base for supplementation programs of this age group.[11]

In contrast, VA deficiency during pregnancy was, until recently, a largely unexplored area of public health interest[2]. Early work in the 1930's by Mellanby and Green identified a potential role for VA (in the form of cod liver oil) to reduce puerperal septicaemia, although little follow-up work continued for the next half century.[12–14] Four main developments contributed to a re-awakening of interest in the potential role of VA supplementation during pregnancy (1) Recognition that maternal supplementation during pregnancy and lactation could be an opportunity to improve the VA status and health of infants (2) Findings from a large trial in Nepal that VA and -C supplementation during pregnancy was associated with a 40% reduction in risk of pregnancy-related mortality[15] (3) Observations that low serum retinol levels were associated with increased risk of mother to child transmission of HIV, and the hypothesis that VA, by virtue of its role in epithelial integrity or immune-modulating properties might help to reduce transmission[16] (4) Growing recognition that VA might have a role in improving hematologic status during pregnancy.[17]

The objective of our review was to consolidate knowledge about the effects of supplementation on multiple outcomes related to maternal, perinatal, and infant health to inform policy in low income countries and to identify research priorities.

Methods

We searched the literature to identify trials, intervention studies, and quasi experimental studies isolating the effect of supplementation with VA and/or carotenoids during pregnancy and outcomes shown in Table 1. We searched NLM Pubmed and the Cochrane Library using search strategies outlined in Supplementary Table 1 in November 2010 and updated

the search in June, 2011. We also hand-searched reports from major micronutrient conferences as well as the bibliographies of relevant reviews and studies.

An initial screening of all titles and abstracts was undertaken to exclude (1) non-human studies, (2) studies not in English, French, or Spanish (3) Reviews, case reports, commentaries and other papers not reporting primary data (4) Topics clearly not relevant to the exposure/outcome relationships (5) papers with research designs that clearly could not isolate effects of VA/carotenoids (for example studies of cod-liver oil). One reviewer (ATL) reviewed the original full papers of studies that could not be excluded based on title and abstract review.

Data were extracted using a standard spreadsheet developed for other reviews in this supplement using best available published data. The authors of one paper provided a clarification of data on birth outcomes in response to requests (personal communication, Anna Coutsoudis (4/11/2011).[8] The quality and the potential for bias of each study was using a slightly modified version of the Child Health Epidemiology Reference Group's GRADE tool.[18]

Meta-analysis was used to generate effect estimates for outcomes in which there was more than one study with sufficient data appropriate to enable pooling. We excluded studies that were classified as "Very low" using the GRADE criteria. Studies that randomized VA during both pregnancy and lactation were eligible for inclusion, recognizing that attribution of effects of VA supplementation specifically during pregnancy could not be made for post-partum outcomes.

Review Manager 5.1 was used for all data analysis.[19] Dichotomous outcomes were expressed as risk ratios, and continuous outcomes were expressed as mean differences with 95% confidence intervals. Inverse variance weights were used in the pooling of data. For analyses that included cluster-randomized trials, we included outcomes for which cluster-adjusted estimates were reported and used the generic inverse-variance method.[19] Heterogeneity across studies within outcomes was explored using visual inspection of the distribution of effect estimates, I^2 values, and tested for using chi-square tests for heterogeneity using a p-value of less than 0.10 to denote statistical significance. Data was pooled using a fixed effects model except in cases in which statistically significant heterogeneity was present in which case a random effects (RE) model was used. Recognizing the potential for heterogeneity across studies, we considered baseline VA status, supplement form and dosage, HIV prevalence as *a priori* sources of heterogeneity. We present disaggregated effect estimates in addition to pooled effect estimates for outcomes in which trials in HIV-positive women were available in order to facilitate policy decisions for populations with high or low HIV prevalence.

A number of trials used multifactorial designs with multiple treatment arms containing VA, -C, or both. [9, 15, 20–24] For purposes of data extraction and meta analyses we treated these studies as follows: (1) For papers in which results were presented for pooled treatment arms containing VA/ -C vs. those not containing VA/ -C, we also pooled data in this manner (2) For studies using the same factorial design where two separate comparisons isolating the effects were possible (i.e. VA vs. placebo and VA+multivitamins vs. multivitamins alone), data were entered for each comparison and treated as separate studies (3) For studies with multiple arms testing different dosages of VA but only 1 placebo group, data from the two treatment arms was combined when possible.

Results

Literature search and identification of studies

After removing duplicates, our search resulted in 923 articles from which 23 eligible studies were identified with at least one outcome of relevance. Of these, six were ranked "Very Low" on the GRADE criteria and were therefore excluded from meta-analyses (Supplementary Table 2). Our search of the abstracts from key micronutrient conferences led to the identification of several abstracts of relevance although none contained sufficient detail to enable evaluation of study quality or inclusion in pooled analysis.

Study characteristics

Key characteristics of studies included in this review are presented in Table 2. Three large cluster randomized controlled trials (RCT's) were included: trials from Nepal and Bangladesh assessed the independent and pooled effects of both VA and -C on maternal and neonatal mortality in addition to other outcomes, while the other, from Ghana, examined the effects of VA alone.[15, 25, 26] Of the 17 studies included in the meta-analyses, 10 were conducted in Asian settings and seven in Africa and with the exception of one study from China and one from South Africa all were conducted in low income countries.[21, 27] Three RCT's were undertaken in HIV-positive pregnant women in Africa prior to the availability of anti-retroviral therapy, and had the primary objective of exploring the effect of VA supplementation on mother to child transmission of HIV, but also reported on a number of birth and child health outcomes.[9, 28, 29]

Dosage and form of supplements varied across the studies from a weekly dose providing the equivalent of a daily dose of 3333 IU VA to 10,000 IU per day. Two of the studies in HIV+ women included intervention arms with both a supplement of 5000 IU VA per day and 30 mg -C as well as a 200,000 IU dose of VA at delivery.[9, 27] Two studies explored the effects of lycopene supplementation, one of which provided 2 mg daily while the other provided 4 mg per day, although both of these studies were judged to be of low GRADE quality (Supplementary Table 2).

Outcomes

Small-for-gestational age and birthweight—The overall effects of VA on small-for-gestational age (SGA), and very low birthweight (<2.0 kg) were null, and that for low birthweight (<2.5kg) was null but had a trend towards significance, RR=0.83, [0.67, 1.01] (Figure 1). The subgroup of three studies conducted in HIV+ populations showed a significant reduction in risk of LBW, RR=0.79 [0.64, 0.99]. No significant effects of VA on mean birthweight were apparent in meta-analysis (**Evaluation of the quality of individual trials for potential inclusion in the meta-analysis using GRADE criteria** Supplementary Figure 1) or in a large sub-study from the Nepal trial published only in abstract form,[30] and lycopene supplementation did not have a significant effect on mean birthweight in pooled analysis (Supplementary Figure 2).

Effect on preterm birth—No significant overall effect was found of VA on preterm birth (<37 weeks) or early preterm birth (<34 weeks) (Figure 2). There was substantial heterogeneity within the HIV+ subgroup for preterm birth (I^2=76%, p=0.04), and in the overall effect estimate for early preterm birth (I^2=78%, p=0.03). A significant 33% reduction in the prevalence of preterm birth and a 66% reduction in early preterm birth among women was observed in the South African study, but no other individual trials showed statistically significant effects.[8] No effect of lycopene supplementation was found on mean gestational age at delivery (Supplementary Figure 3) although substantial

heterogeneity was observed (I^2=94%, P<0.0001) and one included trial reported an increased risk of preterm birth compared with placebo (10.4% vs. 1.2%, p=0.02).[31, 32]

Effect on stillbirth, miscarriage, and fetal death—The overall effect estimates for supplementation with VA or -C on stillbirth, (Supplementary Figure 4) miscarriage (Supplementary Figure 5), and fetal loss (Supplementary Figure 6) were all null, as were each of the individual studies contributing to the estimates.

Maternal mortality, morbidity, and birth complications—Three large double-blinded, cluster-randomized, placebo-controlled trials assessed the impact of VA supplementation on all-cause pregnancy-related mortality up to 42 days postpartum.[15, 25, 26] The combined effect estimate from these studies (Figure 3) indicated a null overall effect (RR=0.86 [0.60, 1.24]), although significant heterogeneity across the two studies was apparent (I^2=74%, p=0.02), with the Nepal study exhibiting a 44% decrease in maternal mortality and the Ghana and Bangladesh studies showing no significant effect. The trial in Ghana reported no significant difference in risk of hospital admission with diagnosis of one or more severe pregnancy-related conditions within 6 weeks postpartum between the VA and placebo groups (RR=0.98 [0.89, 1.09]).[25] Both the Nepal and Bangladesh trials collected information on cause of death through verbal autopsy but this information was not pooled due to a lack of information about the design effect from the cluster-randomized design. Although one trial with lycopene found a significant protective effect of supplementation on pre-eclampsia risk, the summary estimate from two studies was null (Supplementary Figure 7). Two studies examined risk of delivery using Caesarian section as an outcome, one with VA/ C and the other with lycopene and neither found a significant effect of supplementation[8, 31]. One study examined the effect of lycopene supplementation in pregnancy and found no effect on incidence of traumatic or atonic hemorrhage, or both.[31]

Maternal anemia and hemoglobin—Supplementation with any form of VA or -C was found to significantly (p<0.05) reduce the risk of anemia (Hb<11g/dL) at follow-up during pregnancy by 19% (Figure 4). Three of the individual trials found a significant protective effect, and there was consistency in the direction of effect measures for all of the trials including those with null results. However, there was significant heterogeneity in the effect estimate which completely resolved in a sensitivity analysis that excluded the intervention and comparison arms of the factorial trial by Suharno providing concomitant iron supplementation (RR=0.86 [0.79, 0.93], I^2=0, p for heterogeneity=0.42).[22] The pooled analysis of studies with severe anemia as an outcome indicated no statistically significant effect of VA supplementation RR=0.93 [0.59, 1.45] (Supplementary Figure 8).

Average follow-up measures of mean hemoglobin assessed after supplementation during pregnancy were found to be significantly higher among women supplemented with VA by 0.35 g/dL [95% CI 0.24, 0.45] (Supplementary Figure 9) and a change in 0.19 g/dL [95% CI 0.06, 0.33] among studies reporting change in hemoglobin levels (Supplementary Figure 10). However, no differences in maternal hemoglobin were observed in group comparisons of women at 4–6 months postpartum (Supplementary Figure 11).

Infant and young child hemoglobin and anemia—Two studies, both in HIV positive populations examined the effect of maternal VA supplementation on risk of anemia (Hb<11.0g/dL) among infants and young children suggested a trend towards a protective effect (RR= 0.71 [0.49, 1.03], p=0.07) Supplementary Figure 12, although considerable heterogeneity was evident (I^2=74%, p=0.05) [9, 29] Sensitivity analyses using data on any anemia during an average follow-up of 28 months from the Tanzanian trial rather than time to first episode of anemia led to an attenuation of the effect estimate (RR=0.89 [95% CI

0.74, 1.07], p=0.21).[33] No effect of VA supplementation on mean infant hemoglobin was observed at 4–6 months. (Supplementary Figure 13).

Neonatal and infant mortality, morbidity, and growth—We found strong evidence that maternal VA supplementation during pregnancy does not have an overall effect on mortality during infancy or the neonatal period (Figure 5). The pooled effect estimates were null and weighted strongly by the large cluster randomized trials, none of which suggested a significant effect. An analyses from the Nepal trial stratified by maternal night blindness status during pregnancy suggested that VA supplementation might reduce risk of mortality specifically among infants born to night-blind women although -C did not appear to be as efficacious.[5] The Bangladesh trial was the only one that we identified with cause-specific infant mortality and found no differences across treatment groups.[26]

Assessment methods for neonatal and infant morbidity differed greatly across trials limiting the utility of pooling. A trial in Indonesia found no significant effect on maternal VA supplementation during pregnancy on incidence of diarrhea, cough, difficulty breathing or other morbidity outcomes over the first year of life.[34] In the Tanzania trial of HIV-positive women, VA+ -C supplementation during pregnancy and in a large dose postpartum was found to significantly reduce risk of cough and rapid respiratory rate among offspring by 31%, (RR=0.69 [0.49–0.96]), but no effect on diarrhea was observed.[35] VA+ -C supplementation alone was also associated with a borderline significant 63% reduction in incidence of clinical malaria in the same study (RR=0.37 [0.13, 1.04], P = 0.06) compared with placebo but no significant effects of supplementation on malarial mortality were observed (RR=0.65 [0.29, 1.46]. [35, 36] In findings from the Nepal trial, published in abstract form, no significant supplementation group differences were observed in 7-day recalls of diarrhea, dysentery, high fever, or cough for infants at 3 or 6 months of life.[37] Similarly in Indonesia, no significant effect of -C was observed on first occurrence of cough or diarrhea.[38]

A number of studies have reported on anthropometric measures taken during the first year of life although differences in reporting of indicators constrained our ability to incorporate findings into pooled analyses.[20, 29, 39, 40] We found little evidence of an effect of VA or -C supplementation on weight-for-age or height-for-age z score (Supplementary Figure 14, Supplementary Figure 15). In the Malawi trial, infants of HIV-positive women who received VA during pregnancy had greater attained length and weight at 6 weeks, but these differences did not persist at 14 weeks or 6 months of age. [29]. In a subset of 833 infants from the Nepal study, published in abstract form only, VA supplementation during pregnancy was found to be associated with significantly greater average daily weight and MUAC gain but not length gain from 0–3 months of age, but did not persist at 3–6 months of age, although there was a trend towards greater attained weight in both intervention groups at 6 months.[30]

Mother to child HIV transmission—The overall effect of supplementation with VA or VA/ C on HIV transmission was null, although there was significant heterogeneity for this outcome (I^2=75%, P=0.02) (Figure 6). Examining the individual effects of these trials, the trial from Tanzania showed a significant 35% increased risk of transmission and the remainder were null. [9] Although not eligible for inclusion in our pooled analysis because it tested the effects of maternal and/or infant VA supplementation during the early postpartum period and not supplementation during pregnancy, we also noted findings from the ZVITAMBO trial suggesting increased risk of HIV infection or death among offspring whose mothers received postpartum VA supplementation but who did not receive direct supplementation themselves.[41]

Discussion

IUGR and preterm birth

Some, but not all observational studies have reported that low plasma retinol concentrations are associated with intrauterine growth restriction[42–45]. We found limited evidence to evaluate the effect of VA supplementation on intrauterine growth restriction, and no effect on mean birthweight was observed overall. Our findings of a significant reduction in the risk of LBW specifically among HIV-positive women are in contrast to previous meta-analyses which reported a null effect. [46, 47] Our analysis differed in two ways: (1) We excluded a trial of multi-micronutrient supplementation which did not isolate the effect of VA and (2) We requested and included additional data from one of the studies in which the published denominators were unclear. [8, 9, 48] We therefore believe our effect estimates provide the most accurate representation of the pooled effects of VA/ -C supplementation during pregnancy on risk of LBW incidence among HIV positive women to date. It remains unclear whether differences in the effect of VA supplementation on LBW incidence among HIV-positive women are the result of a reduction in IUGR, preterm birth, or both, as the pooled estimates of the effects on both of these components of LBW were null.[8] The trial from Malawi which showed a protective effect did use a higher dose of retinol (10,000 IU) than other studies and did not include high dose -C present in the other two trials although there are also potential contextual differences that might explain the strength of the effect [9, 29, 36, 49].

All but one study suggested that VA or -C supplementation does not influence risk of preterm birth. The one study to show a protective effect of supplementation on preterm birth also noted that this effect disappeared when excluding multiple pregnancies. [8] Interestingly, the large trial in Nepal found a heightened risk of twinning associated with VA/ C supplementation, a phenomenon that might be expected to increase the risk of adverse perinatal outcomes including preterm birth, although no difference in risk of preterm birth was observed overall. [50]

Stillbirth, miscarriage, and fetal loss

Our finding of no adverse effect of VA supplementation on outcomes related to fetal loss supports conclusions that VA supplementation appears to be safe throughout pregnancy at levels at or below the amounts tested in the large trials (23,000 IU/week and 10,000 IU per day), although we did not specifically examine birth defects as an outcome.

Maternal all-cause pregnancy-related mortality

The World Health Organization currently does not recommend VA supplementation during pregnancy for the prevention of maternal and infant morbidity and mortality, but does recommend supplementation for the prevention of night blindness in areas where VA deficiency is a serious public health problem.[51] Our findings are supportive of this recommendation and are also consistent with those of the recent Cochrane review, though our analysis differed in that we also included the subsequently published trial from Bangladesh and omitted an early trial of cod-liver oil on the grounds that it did not isolate the effects of vitamin A.[12, 24, 26]

Substantial heterogeneity was observed for the effect estimate on maternal mortality, and reflects the contrast of protective effects observed in Nepal against null findings observed in Bangladesh and Ghana. The heterogeneity observed across these three large and well conducted trials is difficult to explain. Differences in compliance rates are an unlikely explanation, as all studies assessed and reported high compliance.[15, 25, 26] It has been argued that findings in the Nepal study may have arisen by chance, based primarily on observations

that a large number of deaths were attributable to injury and other causes in the verbal autopsy.[25]

Other contextual differences related to the prevalence of VA deficiency or pregnancy-related mortality might be responsible in some way for contrasting effects.[52] The trial population in Nepal appears to have been worse off than those in Ghana and Bangladesh in many ways including having substantially higher rates of pregnancy related mortality (704, 377, and 231 deaths per 100,000 pregnancies respectively), higher presumed prevalence of wasting malnutrition, and lower intake of eggs and fish compared with Bangladesh.[15, 25, 53, 54] Although there was little reported information on availability of health services in the trial reports, it was noted that a greater proportion of deliveries in Bangladesh were attended by traditional or skilled health workers than in Nepal.[26]

Moderate VA deficiency (plasma retinol <0.7 µmol/L) was also most prevalent in Nepal (19%) followed by Ghana (15%) and Bangladesh (8%).[15, 25, 53] While VA, but not C, supplementation appeared to lead to significant reductions in moderate VA deficiency in Bangladesh and Nepal, findings from Ghana were counterintuitive: A greater proportion of women in the VA arm of the trial had moderate VA deficiency (<0.70 µmol/L) compared with those in the placebo arm (25% vs. 15.4%, p=0.048). Such findings are difficult to explain as investigators reported good compliance with assigned regimens, although serum retinol is known to be an imperfect measure of VA status as it is homeostatically regulated and affected by infection and other factors unrelated to deficiency.[55]

The prevalence of night blindness during pregnancy in the Nepal and Bangladesh trials was similar (about 9–10%), while night blindness was not measured in the Ghana trial but is reportedly uncommon. [25] Night-blind women in the Nepal trial were observed to have a five-fold greater risk of death due to infection-related causes compared with non-night blind women and much of the mortality risk was found to be attenuated by supplementation with VA or C.[56] In the Bangladesh trial, all women who were identified as night blind when screened at week 28 of gestation were treated with VA according to WHO protocols for ethical reasons.[57] If mortality risk was concentrated among such women in Bangladesh, as it appeared to have been in Nepal, it is possible that this may have led to an attenuation of any beneficial effects. In any case, findings from the Nepal study underscore the importance of recommendations that all night blind women be treated with VA.

Maternal and child hemoglobin and anemia

Cross-sectional surveys and observational studies in women and in children often show correlations between anemia and VA deficiency and improving VA status in deficient populations typically results in improvements in anemia.[58–60] Our finding that supplementation with VA led to an average increase in mean hemoglobin levels on the order of approximately 0.2 g/dL is consistent with previous estimates that VA supplementation of deficient populations can be expected to raise hemoglobin concentrations by 0.2–1.0 g/dL over a period greater two weeks.[59] While not all intervention studies included in our meta-analysis showed a statistically significant reduction in anemia risk, the direction of effect was consistent across all studies. Most of the studies we identified were conducted in trial populations that first screened as anemic and there appeared to be a slightly greater effect of VA supplementation on hemoglobin in those populations. All but two of the studies we identified with outcomes related to maternal hemoglobin or anemia provided iron to all women, so it was not possible to examine potential synergistic effects of VA in the presence or absence of iron supplementation.

The mechanisms through which VA affects anemia remain largely unclear, though a number of hypotheses have been proposed including (1) a potential role of VA in mobilizing iron

stores from the liver (2) increasing erythropoiesis (3) decreasing the "anemia of inflammation" by increasing circulating iron through reducing infection and (4) increasing iron absorption.[59, 61] Studies of the effects of VA supplementation on concentrations of erythropoietin, a hormone that stimulates production of red blood cells by the bone marrow, have been mixed, with one in pregnant women in Malawi showing no effect, another in preschool aged children in a malarial area of Tanzania a showing an decrease in concentrations, and a third in a non-malarial endemic area showing an increase in erythropoietin concentrations[62–64].

Although we did not observe a statistically significant improvement in neonatal/infant anemia associated with supplementation in our pooled analysis of two trials of HIV+ women, a trend toward statistical significance did suggest the possibility of such an effect. However, a previous study in Zimbabwe noted no effect of high dose VA supplementation (400,000 IU) to women postpartum or 50,000 IU to infants on infant hemoglobin or anemia, and another trial from Indonesia noted a similar content of iron in breastmilk in women who were supplemented with -C vs. those who were not[65, 66]. It therefore seems likely that any benefits of VA supplementation during pregnancy on infant hemoglobin are more likely to be the result of improving the iron endowment at birth rather than through breastmilk transfer of iron or VA, and that these benefits probably decrease over time. In a sub-study of 728 infants of mothers participating in the large Nepal trial (published in abstract form), a 2 g/L increase in infant hemoglobin at 3 months was observed in the intervention group relative to controls suggesting that it is possible that effects may last at least this long.[67]

Neonatal and Infant mortality, morbidity, and growth

Pooled estimates for neonatal and infant mortality provide strong evidence that VA/ C supplementation during pregnancy at the doses tested does not appear to reduce neonatal or infant mortality. This is consistent with a meta-analysis showing no effect of maternal postpartum supplementation on mortality, although possible benefits of neonatal supplementation have not been ruled out and several trials are underway to test this hypothesis.[68, 69] As with maternal mortality, findings of an effect of supplementation on infant mortality specifically within the subset of infants born to night blind women support recommendations that this condition be treated with VA supplements.[5]

While VA is known to have an effect on child growth, the precise impact has been difficult to quantify, as VA deficiency often occurs in conjunction with other growth-limiting deficiencies which are often the true "growth-limiting factor."[6] We found little evidence to suggest that VA supplementation during pregnancy affects linear growth or weight gain during infancy, though one limitation of most of the studies we identified through our search was that they examined the effect of supplementation on mean growth rather than indicators more reflective of growth faltering,

HIV transmission

Trials of VA supplementation during pregnancy on risk of HIV transmission from mother to child were initiated based on evidence from observational studies that low maternal serum retinol was associated with increased risk of infant mortality, increased transmission of HIV from mother to child, and greater concentrations of HIV-1 in breast milk and genital tract secretions.[8, 10, 16, 29, 41, 43, 70–73] None of these trials showed a reduction in HIV transmission associated with VA supplementation and the trial in Tanzania suggested a greater increase associated with supplementation during pregnancy and lactation, a finding that was supported by a trial in Zimbabwe of high dose postpartum and/or infant supplementation.[41, 71]

A number of plausible mechanisms have been proposed for potential increased transmission[74]. Evidence from a prospective cohort study in the United States suggested a U-shaped relationship between dietary intake of VA and HIV disease progression and mortality.[75, 76] Some in-vitro studies suggest that VA could increase replication of HIV-1 and increase susceptibility of monocytes and macrophages to HIV infection through increased expression of CCR5 receptors.[77] Recent evidence from the Tanzanian trial showed that VA/ C supplementation was associated with increased risk of subclinical mastitis and increased HIV viral load in breast-milk.[78, 79] Thus, caution is warranted before initiating VA supplementation programs to pregnant women in HIV endemic areas.

Limitations

We searched multiple sources including conference abstract books for relevant reviews but it is possible that we may have missed relevant studies or that publication bias may have influenced the results of our meta-analysis. Our analysis assumes that pooling of different forms and dosages of vitamin A across different settings and contexts is appropriate—it is possible that different forms of VA may have different effects depending on the extent of deficiency and other contextual factors. While there are undoubtedly many different plausible explanations for apparent heterogeneity in results for some outcomes, our ability to identify sources of heterogeneity was limited by the small number of published studies. The recent Cochrane review on maternal vitamin A supplementation during pregnancy provides complementary disaggregated analysis to ours that may be useful in examining sources of heterogeneity including by concomitant micronutrient supplementation, dosage, and duration of intervention.[80]

Conclusions and future research directions

Our review examined the effects of VA/ C supplementation on a broad range of adverse perinatal, maternal, and neonatal outcomes prevalent in low income countries. In pooled analysis, we found little evidence of an overall effect of VA supplementation on either maternal or neonatal/infant mortality although we found significant heterogeneity in estimates of the effect on maternal mortality. VA/ C supplementation appears to also improve hematologic status of women during pregnancy in the presence of concomitant supplementation with iron and folate. Supplementation may also reduce risk of LBW among HIV-positive women, although in areas of high HIV prevalence these benefits should be weighed against the potential risk of increased risk of transmission from mother to child. Findings of no adverse effect on outcomes including stillbirth, fetal loss, miscarriage, support the safety of supplements at levels tested. The evidence level for some outcomes remains low or moderate, and more studies are needed to be able to better understand potential sources of heterogeneity potentially attributable to dosage, HIV status, VA status, interaction with other nutrients, and other contextual factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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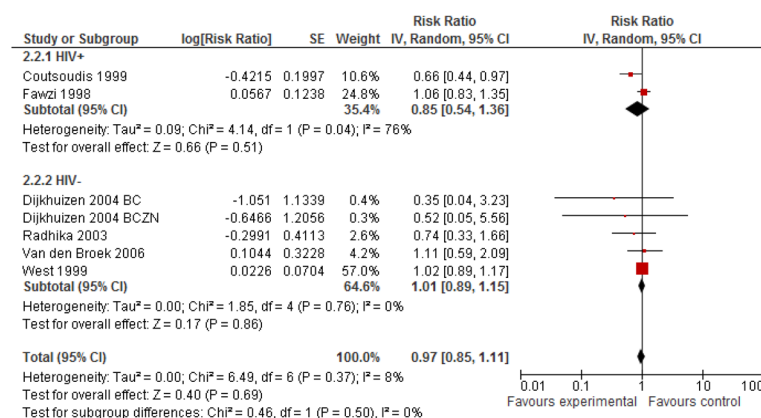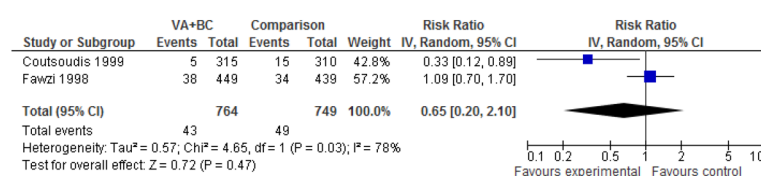
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Small for gestational age
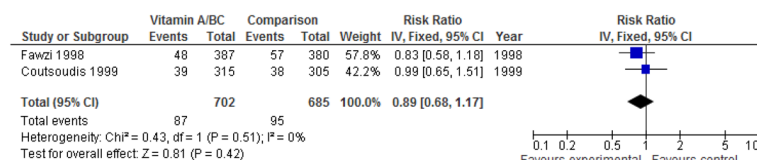
Low birthweight (<2.5 kg)
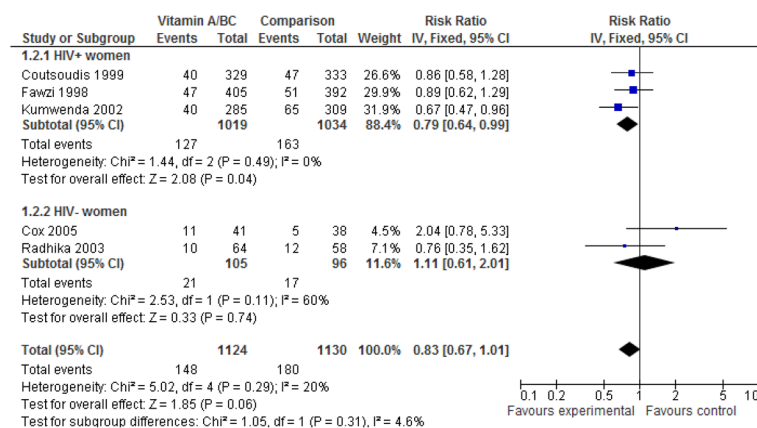
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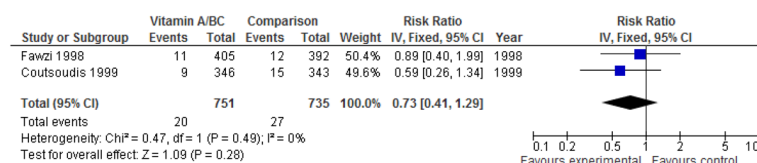
Figure 1.
Forest plot of the effect of vitamin A/ -C supplementation during pregnancy on small for gestational age, low birthweight (<2.5 kg), and very low birthweight (<2.0 kg)

Preterm birth

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
2.2.1 HIV+					
Coutsoudis 1999	-0.4215	0.1997	10.6%	0.66 [0.44, 0.97]	
Fawzi 1998	0.0567	0.1238	24.8%	1.06 [0.83, 1.35]	
Subtotal (95% CI)			35.4%	0.85 [0.54, 1.36]	
Heterogeneity: Tau² = 0.09; Chi² = 4.14, df = 1 (P = 0.04); I² = 76%					
Test for overall effect: Z = 0.66 (P = 0.51)					
2.2.2 HIV-					
Dijkhuizen 2004 BC	-1.051	1.1339	0.4%	0.35 [0.04, 3.23]	
Dijkhuizen 2004 BCZN	-0.6466	1.2056	0.3%	0.52 [0.05, 5.56]	
Radhika 2003	-0.2991	0.4113	2.6%	0.74 [0.33, 1.66]	
Van den Broek 2006	0.1044	0.3228	4.2%	1.11 [0.59, 2.09]	
West 1999	0.0226	0.0704	57.0%	1.02 [0.89, 1.17]	
Subtotal (95% CI)			64.6%	1.01 [0.89, 1.15]	
Heterogeneity: Tau² = 0.00; Chi² = 1.85, df = 4 (P = 0.76); I² = 0%					
Test for overall effect: Z = 0.17 (P = 0.86)					
Total (95% CI)			100.0%	0.97 [0.85, 1.11]	
Heterogeneity: Tau² = 0.00; Chi² = 6.49, df = 6 (P = 0.37); I² = 8%					
Test for overall effect: Z = 0.40 (P = 0.69)					
Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0%					

0.01 0.1 1 10 100
Favours experimental Favours control

Early preterm birth (<34 weeks)

Study or Subgroup	VA+BC Events	Total	Comparison Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Coutsoudis 1999	5	315	15	310	42.8%	0.33 [0.12, 0.89]	
Fawzi 1998	38	449	34	439	57.2%	1.09 [0.70, 1.70]	
Total (95% CI)		764		749	100.0%	0.65 [0.20, 2.10]	
Total events	43		49				
Heterogeneity: Tau² = 0.57; Chi² = 4.65, df = 1 (P = 0.03); I² = 78%							
Test for overall effect: Z = 0.72 (P = 0.47)							

0.1 0.2 0.5 1 2 5 10
Favours experimental Favours control

Figure 2.
Forest plot of the effect of vitamin A/ -C supplementation during pregnancy on preterm birth (<37 weeks gestational age) and early preterm birth (<34 weeks)
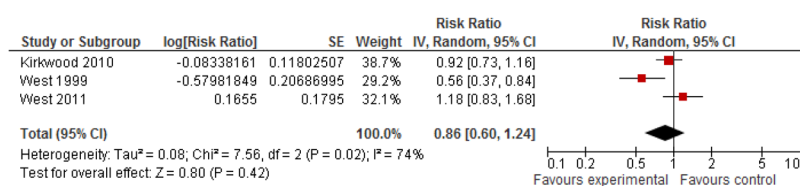
Figure 3.
Forest plot of the effect of vitamin A/ -C supplementation during pregnancy on maternal pregnancy-related mortality
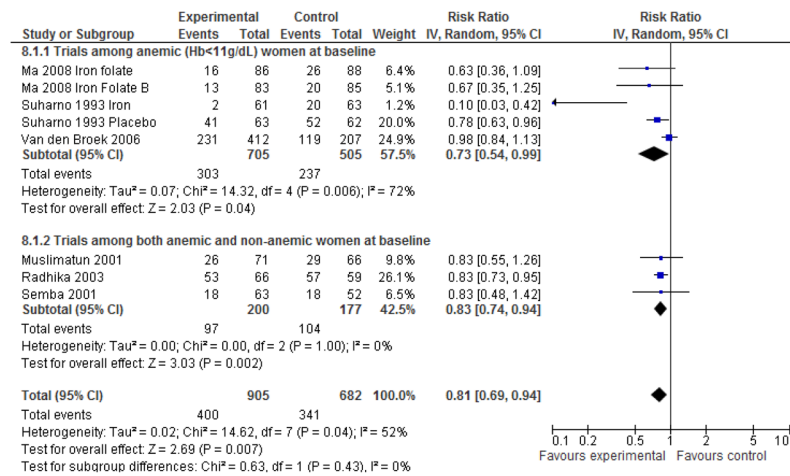
Figure 4.
Forest plot of the effect of vitamin A/ -C supplementation during pregnancy on anemia
(Hb<110 g/L) during pregnancy

Neonatal (<4 or 6 weeks) mortality
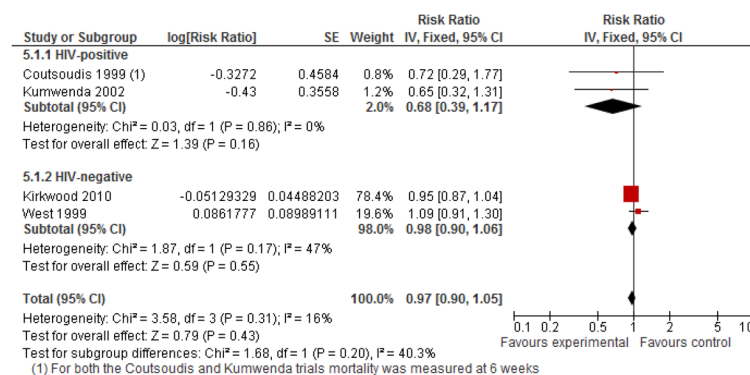
Infant and neonatal mortality
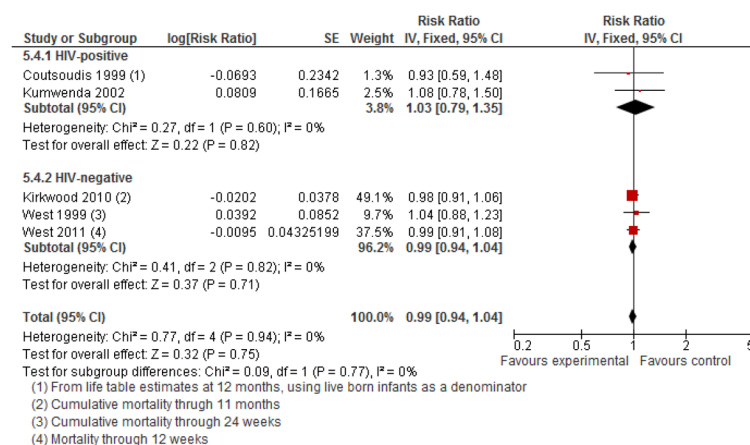
Figure 5.
Forest plot of the effect of vitamin A/ -C supplementation during pregnancy on neonatal and infant mortality

Study or Subgroup	Vit A or Vit A/BC Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Coutsoudis 1999	70	319	70	313	30.9%	0.98 [0.73, 1.31]	
Fawzi 1998 (1)	155	453	113	445	36.7%	1.35 [1.10, 1.65]	
Kumwenda 2002	67	242	82	250	32.4%	0.84 [0.64, 1.11]	
Total (95% CI)		1014		1008	100.0%	1.05 [0.78, 1.41]	
Total events	292		265				

Heterogeneity: Tau² = 0.05; Chi² = 8.08, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 0.32 (P = 0.75)

Favours experimental   Favours control

(1) HIV status assessed at the latest available time point from each study was used

Figure 6.
Forest plot of the effect of vitamin A/ -C supplementation during pregnancy on HIV transmission from mother to child

Table 1

List of primary and sub-outcomes covered by this review

1	Low birthweight due to intrauterine growth restriction	
	1a	Small for gestational age
	1b	Low birthweight
	1c	Mean birthweight
	1d	Weight gain during pregnancy
	1e	Average heel-crown length at delivery [a]
2	Preterm birth	
	2a	Preterm birth
	2b	Early preterm birth
	2c	Mean gestational age at delivery
3	Neonatal growth, morbidity, and mortality	
	3a	Early infant mortality (first 6 weeks)
4	Infant and child growth, morbidity, and mortality	
	4a	Mean weight [a]
	4b	Mean height [a]
	4c	Low weight-for-age [a]
	4d	Low height-for-age [a]
	4e	All-cause mortality
	4f	Mortality due to measles, diarrhea, ALRI, or malaria [a]
	4g	Mother to child transmission of HIV
	4h	Morbidity (diarrhea, measles, malaria, ALRI) [a]
	4i	Child anemia and mean hemoglobin
5	Maternal mortality and pregnancy complications	
	5a	Mortality (all cause)
	5b	Mortality due to hemorrhage, sepsis, or obstructed labor [a]
	5c	Hospital admissions from complications or C-section [a]
	5d	Pre-eclampsia
6	Maternal nutritional status	

6a Anemia and mean hemoglobin

[a]Indicates outcomes for which sufficient comparable outcomes could not be extracted from more than one study

Table 2

Description of key studies discussed in the paper

Study ID	Country	Population	Intervention	Comments
Banerjee (2009)[31]	India (New Delhi)	Healthy primigravid women with singleton pregnancy gest. wks 12 to 20	Daily oral dose of (1) 2mg lycopene, n=77 (2) placebo tablet of same appearance, n=82 until delivery	Double blind RCT. Inadequate allocation concealment, lack of intent to treat analysis Grade quality: Low
Coutsoudis a (1999)[8, 28]	South Africa (KwaZulu-Natal)	HIV-infected women recruited gest. wks 17–39. Baseline: 30.6% ser. retinol <0.7 μmol	Daily oral dose of (1) VA: 5000 IU retinyl palmitate and 30 mg -C and 200,000 IU VA at delivery. n=368 (2) placebo, n=360.	Double blind RCT. Unclear sequence generation, unclear allocation concealment. Grade quality: High
Cox (2005)[49]	Ghana	Healthy primigravid <gest. 24 wks	Daily oral dose of (1) VA: 10,000 IU RE, n=48 (2) placebo, n=50.	Double blind RCT. Small sample size, Grade quality: Moderate
Dijkhuizen (2004)[20, 38]	Indonesia (West Java)	170 pregnant women. Rural women, gest. age <20 wks	Multifactorial trial of daily (1) 4.5 mg -C (2) 30 mg zinc sulfate (3) 4.5 mg -C+ 30 mg zinc sulfate (4) placebo. All women received iron/folate.	Double blind RCT. Grade quality: Moderate
Fawzi (1998)[9, 10, 33, 35, 36, 40, 71, 78, 81–84]	Tanzania (Dares Salaam)	HIV-1 infected between 12–27 weeks gestation, 34% had ser. retinol <0.7 μmol in 2nd trimester.	Multifactorial trial, daily dose of (1) VA: 30 mg -C plus 5000 IU preformed VA and 1 dose 200,000 IU at delivery, n=272 (2) MV excluding VA+ -C, n=271; (3) MV including VA+ -C and 1 dose 200,000 IU VA at delivery, n=268 (4) Placebo, n=267. All received iron-folate and prophylactic chloroquine phosphate.	Double blind RCT. Adequate sequence generation, allocation concealment. Grade quality: High
Kirkwood (2010)[25]	Ghana	Rural women aged 15–45. Serum retinol 15.4% <0.70 μmol/L; mean serum retinol 1.18 (0.52) μmol/L.	Weekly oral dose of (1) VA: 25,000 IU RE, n=104,484 women, 39,601 pregnancies (2) placebo, n=103,297 women, 39,234 pregnancies	Double blind RCT. High dropout due to movement but results accounting for movement were similar Grade quality: High
Kumwenda (2002)[29]	Malawi (Blantyre)	HIV-infected, enrolled at gest. wks 18–28. 51% ser. retinol <0.7μmol during 2nd trimester.	Daily oral dose of (1) VA : 10,000 IU, n=340 (2) Placebo, n=357. Both groups received 200,000 IU VA at delivery	Double blind RCT. Grade quality: High
Ma (2008)[21]	China (rural)	Anemic (Hb<110g/L) pregnant women, 12–24 wks gestation	Multifactorial trial, women assigned to (1) 60mg iron, n=93 (2) 60 mg iron and 2 mg retinol as retinyl palmitate (≈3636 IU), n=91 (3) 60 mg iron and 1.0 mg riboflavin, n=91 (4) 60 mg iron, 2000 μg retinol, 1.0 mg riboflavin, n=83.	Double blind RCT. Grade quality: High
Muslimatun (2001)[34, 39, 66, 85, 86]	Indonesia (West Java)	16–20 wk pregnant at enrollment, aged 17–35 y, mean baseline serum retinol ≈ 1.01+0.03 μmol/L.	2 arms of relevance (1) VA: Weekly dose of 4800 RE as retinyl acetate (≈14,000 IU) with 60 mg elemental iron and 250 μg folic acid, n=122. (2) Iron and folic acid as above, n=121.	Double blind RCT. Grade quality: High
Radhika (2003)[87]	India (Hyderabad)	Healthy women gest. age 16–24 weeks. Excluded women with recurrent pregnancy loss, prior preterm delivery.	Randomized to (1) Daily sachet of red palm oil containing 2,173 to 2307 μg -C per day (≈3621–3845 IU) (2) identical appearing sachet of groundnut oil provided for 8 weeks starting from 26–28 wks gestation. All women received iron-folate for 100 days and prenatal care.	Randomized trial. Seq. generation and allocation conceal. unclear; blinding unclear. Mean hb at baseline

Study ID	Country	Population	Intervention	Comments
Semba (2001)[64]	Malawi (Blantyre)	HIV-negative pregnant women, gest. age 18–28 wks	Randomized to daily (1) 30 mg elemental iron, 400 µg folate and 3000 µg VA (≈10,000 IU) or (2) iron and folate, as above. Both groups received prenatal care, treatment for STD's, malaria prophylaxis (Fansidar).	higher in red palm oil group than control group. Grade quality: Low Double blind RCT. Grade quality: High
Sharma (2003)[32]	India (New Delhi)	Primigravid women with gest. age 16–20 wks with absence of medical complications	Twice daily oral dose of 1) 2mg lycopene (n=116) (2) placebo tablets of same appearance (n=135)	Double blind RCT. Lack of intent to treat analysis. Grade quality: Low
Suharno (1993)[22]	Indonesia, West Java	Pregnant women with Hb 8.0–10.9 g/dL, gest. age 16–24 weeks.	Randomized to daily (1) Placebo, n=62 (2) VA 2.4 mg retinol as retinyl palmitate (≈4363 IU) (n=63), (3) 60 mg iron as ferrous sulfate and placebo (n=63), (4) VA+Iron (n=63).	Double blind RCT. Not intent to treat (23 participants excluded for taking supplements <8 weeks). Inadequate allocation concealment. Grade quality: Low
Tanumihardjo (2002)[23]	Indonesia, West Java	Women in 2nd or 3rd trimester, mean 17 weeks gestation	Women randomized to (1) Placebo, n=7 (2) 8000 IU vitamin A as retinyl palmitate, n=7 (3) 60 mg ferrous sulfate n=5 (4) VA plus iron as above, n=8.	Double blind RCT. Small sample size. Unclear sequence generation/ allocation concealment. Grade quality: Moderate
Van den Broek (2006)[24]	Malawi	Singleton pregnancies with Hb 5–10.9g/dL enrolled at 12–24 weeks, baseline mean ser. retinol 37.1 (13.7) µg/dL, 7.4% <20 µg/dL.	In addition women were randomised to daily doses of (1) 5000 IU VA (2) 10,000 IU VA or (3) placebo. All women received daily iron-folate and antimalarial prophylaxis.	Double blind RCT. Grade quality: High
West (1999)[3, 5, 15, 30, 37, 50, 56, 88–91]	Nepal (Sarlahi)	Rural married women of reproductive age. 19% with serum retinol <0.70 µmol/l.	Weekly oral dose of (1) 23,300 IU VA (7000 µg RE as retinyl palmitate (n=6,070 pregnancies) (2) 42 mg of all trans -C 7000 µg RE (n=5650 pregnancies) (3) placebo (n=5653 pregnancies).	Double blind RCT. Grade quality: High
West (2011)[26]	Bangladesh (Rangpur district)	Rural women with known pregnancy outcome and vital status recorded at 12 weeks. 7.7% with ser. retinol <0.70 µmol/l	Weekly oral dose of (1) VA (7000 µg RE as retinyl palmitate (23,300 IU), (n=19,806 pregnancies) (2) 42 mg of all trans -C 7000 µg RE, (n=19,998 pregnancies) (3) placebo (n=19,862 pregnancies).	Double blind RCT. in women of reproductive age with 3 arms Grade quality: High

[a] Additional information for preterm, SGA, and birthweight indicators obtained through personal communication with Drs. Coutsoudis and Kuhn (4/11/2011), Abbreviations: VA=vitamin A, gest.=gestational wks.=weeks, ser.=serum, RE=retinol equivalents, -C=Beta-carotene, seq.=sequence

Table 3

Summary of findings and overall assessment of quality of evidence, by outcome

Quality Assessment					Summary of Findings		
No. studies and study design	Heterogeneity of results?	Consistent size of effect?	Generalizable to intervention of interest?	Other sources of bias (e.g., major limitations in study design)	N	Statistical method	Effect estimate [95% CI]
Small for gestational age, Overall quality of evidence grade=Low							
2 RCTs[27,9] (both in HIV positive women)	Low (I²=0%, p=0.51); Neither study showed a significant effect	Both studies null	Both studies provided the same supplement (5,000 IU Vit. A +30 mg - C+postpartum 200,000 IU.	None	1387	RR (IV, Fixed)	0.89 [0.68, 1.17]
Low birthweight <2.5 kg, Overall quality of evidence grade=Low							
5 RCTs[9,27,29,49,87] (3 in HIV + women)	Moderate (I²=20%, p=0.29); 1 study showed significant effect	All but 1 study had protective direction of effect	Different supplements: VA+ C, VA, Palm oil. Iron-folate, malaria prophylaxis varied across trials.	All but one study were of high or moderate grade quality	2254	Risk Ratio (IV, Fixed, 95% CI)	0.83 [0.67, 1.01] HIV+: 0.79 [0.64, 0.99] HIV-: 1.11 [0.61, 2.01]
Very low birthweight <2.0 kg, HIV-positive: Overall quality of evidence grade=Low							
2 RCTs[27,9] (both in HIV-positive women)	Low (I²=0%, p=0.49); Neither study showed a significant effect	Both studies null, effect estimates towards protective	Both used the same supplement (5,000 IU Vit. A +30 mg - C).	None, all were high grade quality	1486	Risk Ratio (IV, Fixed, 95% CI)	0.73 [0.41, 1.29]
Mean birthweight (kg): Overall quality of evidence grade=Moderate							
7 RCTs[9,27,29,49,87,92] (3 in HIV positive women)	High (I²=53%, p=0.05); 2 studies showed significant effects in opposite directions	5 were null, 2 showed opposite effects.	Supplements used included VA, VA + C, C, and Palm oil as a source of C.	All but one study were of high or moderate grade quality	2417	MD IV, Random	0.03 [−0.04, 0.10]kg HIV+: 0.04 [−0.01, 0.08] HIV-: 0.02 [−0.17, 0.21]
Lycopene supplementation on mean birthweight (kg): Overall quality of evidence grade= Very low							
2 RCTs[31,32]	High (I²=65%, p=0.09);	Both studies null, RR's in opposite directions	One study supplemented with 2 mg/day lycopene, the other with 4 mg/ day	Both studies had low grade quality, neither used intent-to treat analysis	410	MD IV Random	0.03 kg [−0.12, 0.18]
Preterm birth <37 weeks: Overall quality of evidence grade=High							
7 RCTs[9,24,27,87,92,93]	Low, (I²=8%, p=0.37)	One study protective, 6 null	Two studies in HIV + women; 5 in HIV-negative; Differences in	All but one study were of high or	19,799[a]	Risk Ratio (IV, Fixed, 95% CI)	Overall 0.99 [0.88, 1.10] HIV+: 0.93 [0.75, 1.14] HIV-: 1.01 [0.89, 1.15]

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Quality Assessment					Summary of Findings		
No. studies and study design	Heterogeneity of results?	Consistent size of effect?	Generalizable to intervention of interest? (supplement type/dosage)	Other sources of bias (e.g., major limitations in study design)	N	Statistical method	Effect estimate [95% CI]
Early preterm birth <34 weeks: Overall quality of evidence grade=Low							
2 RCT's[279] (both in HIV-positive women);	High, (I²=78%, p=0.03);	No, one study protective, one null	Both studies used the same supplement (VA+ C)	moderate quality; Both studies of high GRADE quality	1513	RR IV, Random	HIV+ 0.65 [0.20, 2.11]
Lycopene, mean gestational age at delivery: Overall quality of evidence grade=Very low							
2 RCTs[31,32]	(I²=94%, P<0.0001);	1 null; one positive	1 with 2 mg/day lycopene, the other with 4 mg/day	Both low GRADE quality, neither used intent-to treat analysis	410	MD IV Random	0.40 weeks [−1.1, 1.9]
Stillbirth: Overall quality of evidence grade=High							
5 RCT's (2 HIV +)[9,25,29,88,94]	Low (I²=0%, p=0.98); All studies null	Yes, all studies null	Variation in supplements used; VA, VA+ C,	All studies of high GRADE quality	106,894[a]	RR IV Fixed	1.03 [0.97, 1.10]; HIV+ 1.07 [0.66, 1.74]; HIV− 1.03 [0.97, 1.10]
Fetal loss: Overall quality of evidence grade=High							
7 RCT's (3 HIV +)[9,25,27,29,54,88,94]	Low (I²=0%, p=0.78); All studies null	Yes, all studies null	Variation in supplements used;	All studies of high GRADE quality	113,207[a]	RR IV Fixed	0.99 [0.95, 1.04]; HIV+ 0.92 [0.50, 1.67]; HIV− 0.99 [0.95, 1.04]
Miscarriage: Overall quality of evidence grade=Moderate							
4 RCT's (2 HIV+)[9,24,29,88]	Low (I²=0%, p=0.58); All studies null	Yes, all studies null	Variation in supplements used; VA, C, VA+ C	All studies of high GRADE quality	62,138[a]	RR IV Fixed	0.99 [0.95, 1.04]; HIV+ 0.92 [0.51, 1.67]; HIV− 0.99 [0.95, 1.04]
Maternal pregnancy related mortality: Overall quality of evidence grade=High							
3 RCT's[25,54,93]	High, (I²=74%, p=0.02); 1 study showed protective effect, 2 were null	1 large study protective; others null	Variation in supplements used; VA, VA+ C,	All studies of high GRADE quality	160,690[a]	RR IV Random	0.86 [0.60, 1.24]
Maternal mortality due to sepsis: Overall quality of evidence grade=Low							
2 RCT's[54,93]	Low: (I²=0%, P=0.72)	All studies null	Both were pooled estimates of VA and C arms	All studies of high GRADE quality	81,885[a]	RR IV Fixed	0.67 [0.31, 1.46]
Maternal mortality due to hemorrhage: Overall quality of evidence grade=Low							
2 RCT's[54,93]	Moderate: (I²=44%, p=0.18)	All studies null	Both were pooled estimates of VA and C arms	All studies of high GRADE quality	81,885[a]	RR IV Fixed	1.33 [0.61, 2.91]

Quality Assessment						Summary of Findings	
No. studies and study design	Heterogeneity of results?	Consistent size of effect?	Generalizable to intervention of interest?	Other sources of bias (e.g., major limitations in study design)	N	Statistical method	Effect estimate [95% CI]
Maternal mortality due to eclampsia/pre-eclampsia: Overall quality of evidence grade=Low							
2 RCT's[54, 93]	High; (I²=77%, p=0.04);	All studies null	Both were pooled estimates of VA and C arms	All studies of high GRADE quality	81,885[a]	RR IV Random	1.09 [0.24, 4.88]
Maternal mortality due to infection related causes: Overall quality of evidence grade=Low							
2 RCT's[54, 93]	Low: (I²=9%, p=0.29)	All studies null	Both were pooled estimates of VA and C arms	All studies of high GRADE quality	81,885[a]	RR IV Fixed	0.93 [0.53, 1.61]
Lycopene supplementation on pre-eclampsia: Overall quality of evidence grade=Very low							
2 RCTs[31, 32]	(I²=54%, p=0.14);	1 protective, 1 null	2 mg/day lycopene vs. 4 mg/day	Both low GRADE quality, neither intent-to treat	410	RR IV Fixed	0.71 [0.44, 1.14]
Neonatal and early infant mortality: Overall quality of evidence grade= High							
4 RCT's[25, 27, 29, 88] (2 in HIV-positive women)	Moderate: overall (I²=40.3%, p=0.31); in HIV-negative I²=47%, p=0.17), in HIV– I²=0%, p=0.86).	All studies null.	Variation in supplements used; VA, C, VA+ C,	All studies of high GRADE quality	91,022[a]	RR IV Fixed	0.97 [0.90, 1.05] HIV+: 0.68 [0.39, 1.17] HIV–: 0.98 [0.90, 1.06]
Infant and neonatal mortality: Overall quality of evidence grade=High							
5 RCT's[25, 27, 29, 47, 88]	Low; (I²=0%);	All studies null	Variation in supplements used; VA, C, VA+ C; variation in postpartum supplements.	All studies of high GRADE quality	132,903[a]	RR IV Fixed	0.99 [0.94, 1.04] HIV+: 1.03 [0.79, 1.35] HIV–: 0.99 [0.94, 1.04]
HIV transmission from mother to child: Overall quality of evidence grade=Moderate							
3 RCT's[9, 27, 29]	High; (I²=75%, p=0.02);	2 studies null, 1 study showed significant increase in HIV transmission	Variation in supplements used; two had VA+ C, 1 had VA	All studies of high GRADE quality	2022	RR IV Random	HIV+: 1.05 [0.78, 1.41]
Maternal anemia (Hb<11 g/dL) during follow-up in pregnancy: Overall quality of evidence grade=High							
8 RCT's[b, 21, 22, 24, 64, 86, 87]	High; overall (I²=54%, p=0.03%), (Anemic women I²=74%, p=0.004); (Non anemic women I²=0%)	All studies had effect estimates in a prot. direction 3/8 sig.	Variation in supplements used; VA, Differences in provision of iron-folate supplements	All studies but 2 of high GRADE quality	1587	RR IV Random	0.81 [0.69, 0.94] Anemic: 0.72 [0.53, 0.99] Unscreened for anemia: 0.83 [0.69, 0.95]
Maternal severe anemia <8.0 or 8.5 g/dL) during pregnancy: Overall quality of evidence grade=Low							

Quality Assessment						Summary of Findings	
No. studies and study design	Heterogeneity of results?	Consistent size of effect?	Generalizable to intervention of interest?	Other sources of bias (e.g., major limitations in study design)	N	Statistical method	Effect estimate [95% CI]
3 RCT's[b,21,24]	Low; (I²=0%, p=0.03)	All studies null	Both trials used vitamin A	Both studies of high GRADE quality	961	RR IV Fixed	0.93 [0.60, 1.46]
Mean maternal hemoglobin during follow-up in pregnancy: Overall quality of evidence grade=Moderate							
8 RCT's[b,22–24,49,86,87]	Some; (I²=17%, p=0.29)	All studies null but one factorial trial null where both comparisons showed significantly positive effects	Five studies used vitamin A; one used palm oil. All women except those in placebo arms of two factorial trials received iron folate	All but one study of high grade quality	1034	MD IV Fixed	0.35 [0.24, 0.45]
Change in maternal hemoglobin during pregnancy: Overall quality of evidence grade=Moderate							
8 RCT's[21,24,64,86,87]	Some; (I²=15%)	All studies but the factorial trial null	Variation in supplements used; all had iron-folate	All but one study of high grade quality	1131	MD IV Random	0.19 [0.06, 0.33]
Mean postpartum maternal hemoglobin (4–6 weeks postpartum): Overall quality of evidence grade=Moderate							
4 RCT's[49,86,92]	Low; (I²=0%, p=0.31)	All studies null,	1 study with 2 arms used C, 2 studies used VA	All but one study of high grade quality	365	MD IV FIXED	0.01 [−0.24, 0.25]
Infant anemia: Overall quality of evidence grade=Low							
2 RCT's[29,33] (Both in HIV+ women)	Yes; (I²=74%, p=0.05);	1 study protective, 1 null	Variation in supplements used	All studies of high GRADE quality	894	RR IV Random	HIV+ 0.71 [0.49, 1.03], p=0.07
Infant hemoglobin at 4–6 months (g/dL): Overall quality of evidence grade=Low							
2 RCT's[92,95] (1 factorial)	No; (I²=0%, p=0.96)	All three studies null	Variation in supplements used;	All studies of high GRADE	284	MD IV Fixed	−0.13 [−2.29, 2.03]
Infant weight-for-age z score at 6 months: Overall quality of evidence grade=Low							
2 RCT's[40,92] (2 factorial)	Some; (I²=22%)	Yes, all studies null	Variation in supplements used	All studies of high GRADE	1022	MD IV Fixed	0.07 [−0.07, 0.22]
Infant height-for-age z score at 6 months: Overall quality of evidence grade=Low							
2 RCT's[40,92] (2 factorial)	No; (I²=0%)	Yes, all studies null	Variation in supplements used	All studies of high GRADE	1022	MD IV Fixed	0.01 [−0.12, 0.13]

[a] Effective sample size for analysis is actually smaller due to inclusion of cluster randomized trials in the estimation of variance

[b] Different arms of factorial trials counted as separate trials, prot=protective