Maternal low-dose vitamin A or β-carotene supplementation has no effect on fetal loss and early infant mortality: a randomized cluster trial in Nepal[1–4]

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ABSTRACT

Background: The effect of vitamin A supplementation on the survival of infants aged <6 mo is unclear. Because most infant deaths occur in the first few month of life, maternal supplementation may improve infant survival.

Objectives: The objective was to assess the effect of maternal vitamin A or β-carotene supplementation on fetal loss and survival of infants <6 mo of age.

Design: Married women of reproductive age in 270 wards of Sarlahi district, Nepal, were eligible to participate. Wards were randomly assigned to have women receive weekly doses of 7000 μg retinol equivalents as retinyl palmitate (vitamin A), 42 mg *all-trans*-β-carotene, or placebo. Pregnancies were followed until miscarriage, stillbirth, maternal death, or live birth of one or more infants, who were followed through 24 wk of age.

Results: A total of 43559 women were enrolled; 15832 contributed 17373 pregnancies and 15987 live born infants to the trial. The rate of fetal loss was 92.0/1000 pregnancies in the placebo group, comparable with rates in the vitamin A and β-carotene groups, which had relative risks of 1.06 (95% CI: 0.91, 1.25) and 1.03 (95% CI: 0.87, 1.19), respectively. The 24-wk mortality rate was 70.8/1000 live births in the placebo group, comparable with rates in the vitamin A and β-carotene groups, which had relative risks of 1.05 (95% CI: 0.87, 1.25) and 1.03 (95% CI: 0.86, 1.22), respectively.

Conclusions: Small weekly doses of vitamin A or β-carotene given to women before conception, during pregnancy, and through 24 wk postpartum did not improve fetal or early infant survival in Nepal. *Am J Clin Nutr* 2000;71:1570–6.

KEY WORDS Vitamin A, β-carotene, infant mortality, child survival, fetal loss, maternal supplementation, Nepal, the Nepal Nutrition Intervention Project-Sarlahi Study Group

INTRODUCTION

Vitamin A supplementation via food fortification, periodic large doses, and small, weekly doses has been shown to markedly reduce mortality in children >6 mo of age in Asia and Africa (1–6). Meta-analyses showed a reduction in mortality of ≈25–30% (7, 8). However, the effect of supplementation in infants <6 mo of age is less clear. A large dose of vitamin A given within 48 h of birth was associated with a 64% reduction in infant mortality in Indonesia (9), but supplementation with comparable doses of vitamin A within the first 6 mo of life did not affect the mortality of young infants (5, 10). A recent 3-country trial that assessed the benefits and safety of supplementing infants at 6, 10, and 14 wk of age with 7000 μg retinol equivalents (RE) (25000 IU) vitamin A at each of 3 diphtheria-tetanus-pertussis immunizations also showed no reduction in infant mortality (11). A distinguishing feature of the Indonesian trial was its design and ability to give infants a dose of vitamin A at birth. All of the other studies, by design, failed to reach most infants at the highest risk, the neonatal period.

In a prior study in which large-dose vitamin A supplements given every 4 mo did not affect the mortality of infants during the first 6 mo of life, a high proportion of all deaths occurred among infants who were born and who died between the 4-mo doses (4). Many deaths occurred soon after birth in infants who had not been enrolled in the trial (10). Because so few of these high-

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risk infants would benefit from programs that provide periodic large-dose vitamin A supplements at fixed 4–6-mo intervals and because intrauterine factors have such a strong influence on early infant survival (12), we examined the value of supplementing women during pregnancy and lactation in the hope of improving fetal and early infant vitamin A status, intrauterine growth, and fetal and infant survival.

SUBJECTS AND METHODS

Study design

A randomized cluster placebo-controlled trial was conducted in Sarlahi district, in the south-central plains of Nepal, to assess the effect of small weekly doses of vitamin A or β-carotene in women of childbearing age on fetal and infant mortality. The trial required ≈10 000 pregnancies in the 2 treatment groups combined and 5000 pregnancies in the placebo group to show a 20% reduction in fetal and infant mortality through 6 mo of age with 80% power and a type I error of 5%.

The general design of the study was detailed elsewhere (13). In brief, 30 subdistrict areas (village development communities), each composed of 9 wards, were enrolled in the study. Within each subdistrict, each of the 9 wards were randomly assigned to receive 1 of the 3 treatments, resulting in 90 wards assigned to each treatment group. The treatments consisted of gelatin capsules of identical appearance containing 7000 μg RE as retinyl palmitate, (23 300 IU) preformed vitamin A, 42 mg *all-trans*-β-carotene (7000 μg RE, assuming a 6:1 conversion ratio to retinol after uptake), or a placebo of peanut oil. The nutrient doses were intended to approximate the recommended dietary allowance (RDA) for pregnant or lactating women (14) and were provided weekly. All capsules contained 5 mg *dl*-α-tocopherol (Roche, Basel, Switzerland) and were shipped to Nepal in opaque plastic bottles labeled with 1 of 3 masked, numeric codes. The bottles were relabeled with individual ward numbers that had been assigned to the specific codes.

All married women of childbearing age were eligible for enrollment in the study. These women were identified through a baseline census before dosing. Newly married women were eligible and were enrolled at the time of marriage. However, women who migrated into the study area were not enrolled. Local women were hired and trained to visit the homes of all enrolled women to distribute the weekly supplements. The schedule of visits was such that there were always ≥4 d between each consecutive dose. The 426 distributors recorded pregnancy and vital status, menses in the past week, and receipt of the capsule. Receipt of the capsule was noted only if the distributor observed the woman swallowing the capsule. A woman who was not at home was revisited until such time as there would be <4 d between weekly visits. Capsules were not left for women who were not at home. Pregnancies, miscarriages, stillbirths, and live births were recorded weekly and were based on self-reports. Deaths of women were also noted at this time. Fetal loss was defined as any reported miscarriage, stillbirth, or maternal death during pregnancy. Pregnant women were interviewed at the time they declared themselves pregnant (at an average of 4 mo gestation) and 3 mo later (at an average of 7 mo gestation). These interviews included completion of a 7-d food-frequency questionnaire, a pregnancy history, recording of socioeconomic status, measurement of midupper arm circumference, morbidity, and an activity history. In the event of a miscarriage or stillbirth, a trained interviewer visited the woman and recorded information concerning that event. Women who delivered a live infant were followed and an interview was scheduled at 3 and 6 mo postpartum to assess the health and survival of the infant and mother.

Gestational age was calculated as the difference in time between the outcome of the pregnancy and the last prospectively reported date of a menstrual period. These data were derived by using the history of menses taken weekly if this matched the date of the last menstrual period reported at the second trimester interview. If the date of the last menstrual period (collected by a small number of trained interviewers) did not match the prospective data (collected by a large number of local distributors), then the recalled date of the last menstrual period was used rather than the prospective data, except when the resulting gestational age with this approach did not seem reasonable (eg, a live birth of an infant surviving to 6 mo of age with a gestation of 25 wk).

Pregnant women from a sample of 27 wards (3 village development communities) were enrolled in a more detailed study protocol that included collection of blood specimens by antecubital venipuncture during the first trimester (at ≈4 mo) and again 3 mo postpartum. Blood samples from the infants of these women were collected at 3 mo of age by heel stick. Specimens were centrifuged at 1530 × *g* for 10 min at room temperature and serum was stored and shipped in liquid nitrogen to the Johns Hopkins Center for Human Nutrition Laboratory in Baltimore. Serum specimens were stored at −70°C until analyzed by isocratic HPLC for *all-trans*- retinol and -β-carotene concentrations (15).

The trial was reviewed and received ethical approval from the Joint Committee on Clinical Investigation at the Johns Hopkins School of Medicine, Baltimore, and from the Nepal Health Research Council, Kathmandu, Nepal. The International Teratology Society (Bethesda, MD) also reviewed and approved the proposal. A Data Safety and Monitoring Committee met in Baltimore in November 1996 and in Kathmandu in March 1997 and agreed to continue the study. This committee and the data analysts were unmasked to the treatment codes, but the codes were made available to study investigators only at the end of the trial. Oral, informed consent was given by all individual participants after written consent from each of the village development communities was obtained after discussions with community leaders. Women could refuse capsules or further participation at any time during the trial.

Outcome measures

Pregnancies were defined as those that ended in a live birth or those that ended in a reported miscarriage or stillbirth. In addition, a small proportion of women who reported being pregnant for ≥6 wk but then no longer reported being pregnant or having an outcome were considered to have had a miscarriage. Women who reported being pregnant for <6 wk but had no well-defined outcome were considered to not be pregnant and were not included in the analysis. Only pregnancies reported by women from the last week of July 1994 onward and that ended in an outcome (live birth, stillbirth, miscarriage, or maternal death) before the first week of April 1997 were included in the analysis. These dates were selected to ensure that women generally had the opportunity to receive supplements for ≥20 wk before declaring themselves pregnant and provided enough time for 24 wk of postpartum follow-up before the trial was concluded in early October 1997.

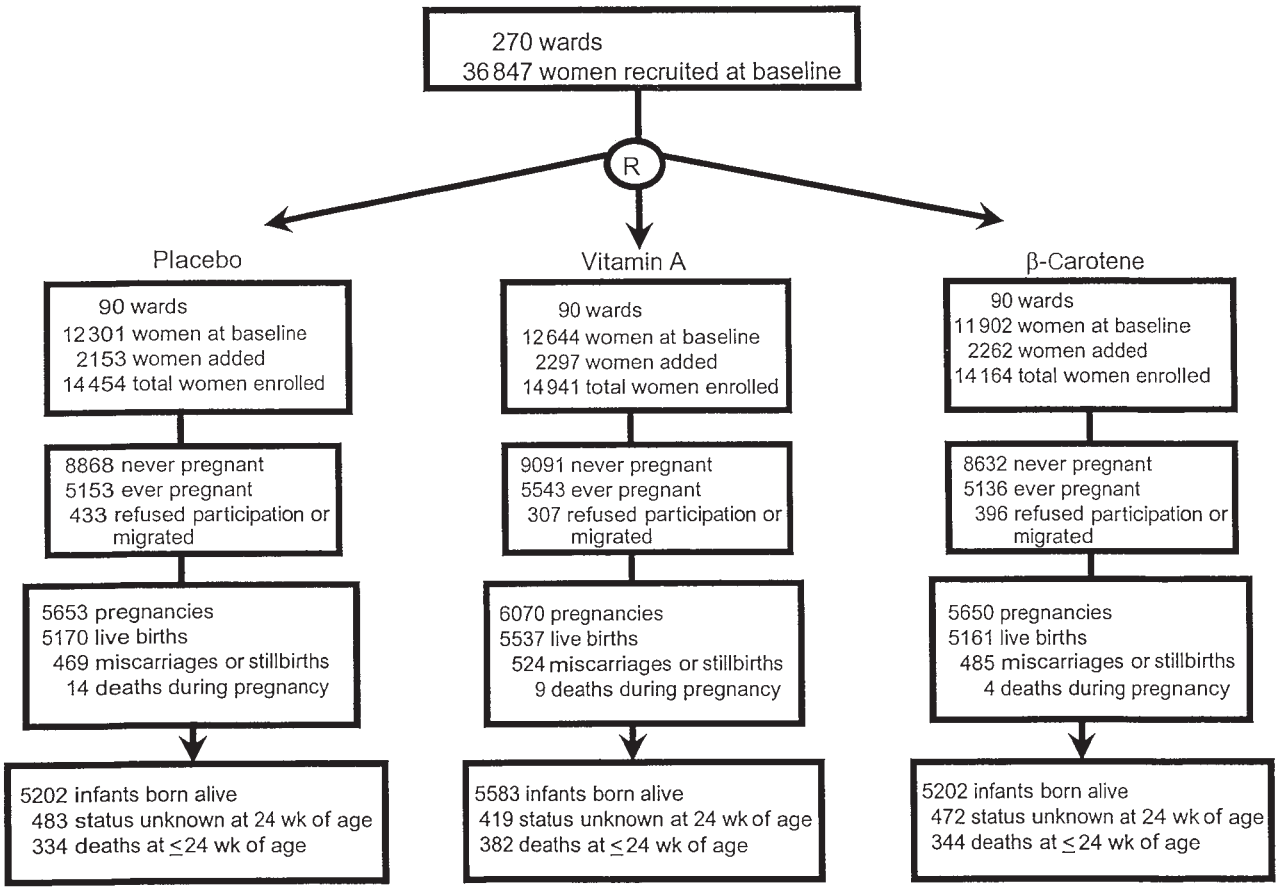

FIGURE 1. Study design and the number of women, number of pregnancies, number of fetal losses, and number of live births in the trial. The number of women and pregnancies is slightly less than that given in reference 13 because all women who had a pregnancy outcome from the last week in July 1994 were included in that analysis. R, randomization.

Statistical analysis

Demographic and socioeconomic characteristics were compared across the 3 treatment groups at the time of the first pregnancy. Compliance with treatment was based on the proportion of eligible doses taken in each pregnancy from 1 mo before conception through 6 mo postpartum or until miscarriage, stillbirth, maternal death, or death of the infant. For a set of twins who died, compliance was calculated as eligible doses from 1 mo before conception to the date of death of the older twin. The analysis was done on an intention-to-treat basis. The 2 main study outcomes were fetal loss (due to miscarriage, stillbirth, or materno-fetal death during pregnancy) and infant mortality up to 24 wk of age. The proportion of pregnancies that resulted in fetal loss was compared across treatment groups by estimating relative risks and 95% CIs. Similarly, the 24-wk infant mortality rates (number of infants who died by 24 wk divided by the total number of live births for which vital status was known at 24 wk) were compared across treatment groups. In addition, neonatal mortality was calculated as the number of deaths of infants <28 d of age/1000 live births. Deaths from 28 d to 24 wk were divided by the number of infants alive at 28 d for whom vital status was known at 24 wk. Treatments were assigned to wards, not to individuals, with stratification by village development community (a subdivision of 9 wards each). The 95% CIs were adjusted for this cluster design by using a generalized-estimating-equations logistic regression model with exchangeable correlation structure in which survival was modeled as a function of the treatment assignment, adjusted for the correlation within the units of randomization (the ward) and stratification (by village development community) (16, 17). If a woman became pregnant more than once during the study, each pregnancy was included in the analysis, as were both infants in twin pairs. An analysis with only the first pregnancy and first infant enrolled in the study produced the same relative risks with 5% wider 95% CIs. SAS (SAS Institute Inc, Cary, NC) was used for the analyses.

RESULTS

A total of 270 wards with 36 847 married women of childbearing age who were enrolled at baseline were randomly assigned to receive vitamin A, β-carotene, or placebo (**Figure 1**). An additional 6712 women who were newly married in or after the last week in July 1994 were enrolled at the time of their marriages. Of the 43 559 women enrolled, 1136 (2.6%) migrated out of the study area or refused to participate in the trial. A total of 15 832 women identified themselves as being pregnant during the period of the study. These women contributed 17 373 pregnancies to the trial (2 women contributed 4 pregnancies, 35 contributed 3 pregnancies, 1465 contributed 2 pregnancies,

TABLE 1
Baseline characteristics of pregnant women (first pregnancies) by treatment group[1]

	Placebo	Vitamin A	β-Carotene
Age			
Number of subjects	4978	5381	4952
<20 y (%)	22.2	21.8	22.6
20–29 y (%)	62.3	61.1	59.0
≥30 y (%)	15.5	17.1	18.4
Midupper arm circumference			
Number of subjects	4465	4865	4466
<21.5 cm (%)	54.8	54.4	53.7
Dietary intake more than once in past week			
Maximum observations	4524	4901	4502
Meat, fish, and eggs (%)	27.1	26.8	26.7
Dairy products (%)	50.6	49.5	52.0
Yellow fruit and vegetables (%)	16.0	16.1	17.1
Dark-green leafy vegetables (%)	36.4	35.7	37.8
Parity			
Number of subjects	4914	5305	4884
Primiparous (%)	26.1	25.4	25.8
Socioeconomic status			
Number of subjects	4734	5135	4714
Literate (%)	15.6	12.8	16.1
Land owners (%)	74.7	73.6	77.5
Delivery status			
Number of subjects	4331	4728	4355
Delivery at a health facility (%)	3.0	3.1	2.9

[1] Numbers of subjects are slightly different for different variables because of missing values.

and the remainder contributed 1 pregnancy). From these pregnancies, there were 15868 live births, 1478 miscarriages or stillbirths, and 27 materno-fetal deaths during pregnancy. There were 119 sets of live born twins, resulting in 15987 live-born infants who were eligible to be followed for survival through 24 wk of age.

The pregnant women in the 3 treatment groups were not significantly different with respect to age, midupper arm circumference, dietary intake, parity, and socioeconomic status (**Table 1**). Of the pregnant women enrolled in the trial, compliance was 3% lower in the β-carotene group than in the other 2 groups. Half of all women who were pregnant received 80% of all possible doses. Of the 87% of women who remained in their home village during pregnancy, half received 88% of all possible doses (≈90% of the RDA), whereas of the 13% who moved to their maternal home during pregnancy, half received 55% of the possible doses of supplements.

In a subsample of 935 women, maternal serum retinol at ≈4 mo gestation was highest in the vitamin A group (1.30 ± 0.33 μmol/L), next highest in the β-carotene group (1.14 ± 0.39 μmol/L), and lowest in the placebo group (1.02 ± 0.35 μmol/L) (13). The means of all 3 groups were significantly different from each other ($P < 0.0001$). Only 2.9% of women in the vitamin A group ($P < 0.0001$) and 13.5% of those in the β-carotene group ($P = 0.0001$) had serum retinol concentrations <0.70 μmol/L; 19.3% of women in the placebo group had concentrations below this amount. In a subsample of 704 of 1215 eligible infants (58%) for whom a heel-stick blood sample was obtained at 3 mo of age, 83% of the placebo group had concentrations <0.70 μmol/L, whereas 62% and 76% of those in the vitamin A and β-carotene groups, respectively, had concentrations below this amount (**Table 2**). The number of infants in the 3 treatment groups was not equal because the assignment to treatment was by community, not by individual, and the subsample was a 10% sample of communities with all infants in those communities being eligible for serum sampling.

There were 144 multiple births in which there was one live infant and one or more stillborn infants (**Table 3**). The prevalence of fetal loss (miscarriages, stillbirths, and materno-fetal deaths during pregnancy) was 92.0/1000 pregnancies in the placebo group, comparable with the rates in the vitamin A and β-carotene groups. The relative risks and 95% CIs indicated no effect of either supplement type on fetal loss. There was no effect of supplementation on the prevalence of preterm birth (gestation <37 wk), which was 282, 314, and 284/1000 pregnancies in the placebo, vitamin A, and β-carotene groups, respectively. However, these rates were relatively high and it is possible that gestational age was underestimated because it appeared that women

TABLE 2
Serum *all-trans*-retinol concentrations in infants at 3 mo of age by treatment group

	Placebo (n = 203)	Vitamin A (n = 224)	β-carotene (n = 277)
all-trans-Retinol (μmol/L)[1]	0.53 ± 0.24	0.66 ± 0.24	0.58 ± 0.24
<0.70 μmol/L (%)[2]	82.8	62.1	76.2

[1] $P < 0.0001$ for comparison of 3 treatment groups (one-way ANOVA), $P < 0.0001$ for comparison of placebo and vitamin A (t test), and $P = 0.07$ for comparison of placebo and β-carotene (t test).

[2] $P < 0.0001$ for comparison of 3 treatment groups (chi-square test with 2 df), $P < 0.0001$ for comparison of placebo and vitamin A (chi-square test with 1 df), and $P = 0.03$ for comparison of placebo and β-carotene (chi-square test with 1 df).

TABLE 3
Effect of maternal supplementation on fetal loss by treatment group

	Placebo	Vitamin A	β-Carotene	Vitamin A or β-carotene
Number of pregnancies	5653	6070	5650	11720
Number of miscarriages or stillbirths	469	524	485	1009
Number of stillbirths with live births	37	59	48	107
Number of maternal deaths during pregnancy	14	9	4	13
Rate of fetal loss[1]	92.0	97.5	95.0	96.3
Relative risk	1.00	1.06	1.03	1.05
95% CI	—	(0.91, 1.25)	(0.87, 1.19)	(0.91, 1.20)

[1] Sum of miscarriages, stillbirths, and materno-fetal deaths during pregnancy/1000 pregnancies.

often mistook vaginal bleeding during early pregnancy for menses. This underestimation might make it harder to observe a treatment effect on the rate of preterm birth if such an effect existed.

Of the 15987 live born infants, 15115 (94.5%) were followed through 28 d of age (**Table 4**). The percentage followed was the same in each group. There were 14613 (91.4%) infants whose vital status was known at 24 wk of age. There was no effect of supplementation on neonatal mortality (birth through 28 d), 28 d through 24 wk mortality, or cumulative 24 wk mortality. The 24-wk infant mortality rate for all 3 treatment groups was 72.5/1000 live births, with 69% of these deaths occurring in the first 28 d of life. There was also no significant difference in the effect of treatment by sex or by whether the delivery occurred at the mother's parental home or not (data not shown).

DISCUSSION

There was no evidence that the RDA of vitamin A, either preformed or as the provitamin β-carotene, offered to a population of malnourished women weekly before conception and during pregnancy reduced the risk of fetal or early infant death. Effects of maternal vitamin A or β-carotene supplementation on fetal loss (≈5% increase), neonatal death (≈9% increase), postneonatal death (≈7% decrease), and cumulative infant mortality before 6 mo of age (≈4% increase) were comparable with and not significantly different from rates observed in the control group. Although maternal supplementation decreased the rate of materno-fetal death by ≈50% (1.11 compared with 2.47 deaths/1000 in the supplemented and placebo groups, respectively) (13), it did not influence the overall effect because fetal loss due to maternal death during pregnancy represents only a small fraction of all fetal wastage (eg, 2.7% in the control group).

Failure to observe an intervention effect on fetal and neonatal survival was unexpected given *1*) the essentialness of vitamin A for embryonic and fetal development and growth (18, 19); *2*) epidemiologic evidence of moderate (20, 21) and responsive (13, 22) maternal vitamin A deficiency in the study population; *3*) clinical studies linking fetal and maternal vitamin A deficiency in malnourished populations (23, 24) and fetal vitamin A deficiency to prematurity or low birth weight (23, 25–29), both strong predictors of infant survival (12); *4*) animal experiments showing increased fetal and neonatal mortality after maternal vitamin A depletion (30); and *5*) higher infant mortality among HIV-negative women with low serum retinol concentrations in Malawi (31).

One explanation for the difference between the results of our randomized trial and the observational data from Malawi may be that the observed association between maternal serum retinol and infant mortality was confounded by factors such as other micronutrient deficiencies that affect both infant mortality and

TABLE 4
Effect of maternal supplementation on early infant mortality by treatment group

	Placebo	Vitamin A	β-Carotene	Vitamin A or β-carotene
Number born alive	5202	5583	5202	10785
Number followed to 28 d	4887	5327	4901	10228
Number of deaths at ≤28 d	224	267	245	512
Neonatal mortality rate[1]	45.8	50.1	50.0	50.1
Relative risk	1.00	1.09	1.09	1.09
95% CI	—	(0.88, 1.34)	(0.87, 1.33)	(0.91, 1.30)
Number alive at 28 d	4663	5060	4656	9716
Number followed to 24 wk	4495	4897	4485	9382
Number of deaths from 28 d to 24 wk	110	115	99	214
Mortality rate from 28 d to 24 wk[2]	24.5	23.5	22.1	22.8
Relative risk	1.00	0.96	0.90	0.93
95% CI	—	(0.73, 1.27)	(0.67, 1.23)	(0.72, 1.20)
Number followed to 24 wk	4719	5164	4730	9894
Number of deaths at ≤24 d	334	382	344	726
Cumulative 24-wk mortality rate[1]	70.8	74.0	72.7	73.4
Relative risk	1.00	1.05	1.03	1.04
95% CI	—	(0.87, 1.25)	(0.86, 1.22)	(0.88, 1.20)

[1] Per 1000 live births.
[2] Per 1000 infants alive at 28 d.

maternal serum retinol. Such confounding is unlikely to have been an issue in this trial because the randomized treatment groups were comparable in a wide variety of important characteristics. However, it is possible that other micronutrient deficiencies, protein-energy malnutrition, or both, among these women could have limited the effect of maternal vitamin A or β-carotene supplementation on early infant mortality. Women in this study were not provided with iron or other supplements other than through regular health care channels, except in the 10% subset of women enrolled in the more detailed clinic study, which included severely anemic women who were treated.

Compliance with treatment was relatively good, with half of all women receiving ≥80% of all possible doses (ie, equivalent to 80% of the RDA). The mean (±SD) proportion of doses taken was 70 ± 30%, and ≈75% of all women received at least half of all possible doses (equivalent to 50% of the RDA). The effect of vitamin A supplementation on night blindness during pregnancy was greater among women with high compliance (22). An analysis stratified by compliance (0–25%, 25–50%, 50–75%, and 75–100%) showed that there was a larger (but not significant) difference in infant serum retinol between the vitamin A and placebo groups among women with high compliance. However, there was no difference in the survival of infants by level of compliance. Hence, compliance altered vitamin A status but not the health outcomes of the infants.

Although there was some improvement in maternal serum retinol concentrations during pregnancy and in the serum retinol concentrations of infants at 3 mo of age, any increase in maternofetal transfer of retinol (32) or neonatal vitamin A intake from breast milk (33) resulting from maternal supplementation may have been insufficient to reduce mortality. Although serum retinol at 3–4 mo of age was significantly higher in infants of vitamin A– and β-carotene–supplemented mothers than in the control group, it remained low (<0.70 μmol/L) for >60% and 75% of the 2 groups, respectively. These values are comparable with those of high-risk preterm newborns (25, 34) and far lower than those of well-nourished, term neonates (28) or older infants elsewhere in Southern Asia whose mothers had received high-potency vitamin A soon after childbirth (35, 36). It is possible that the maximal dose provided was too low to change the vitamin A status enough to affect survival (as suggested by the analysis among high compliers), that other factors limit the ability of vitamin A to promote survival of the fetus and young infant, or that the causes of early infant death are not responsive to maternal supplementation with vitamin A or β-carotene. Previous trials in Nepal, in which young infants were directly given a large dose of vitamin A within the first 6 mo of life, also showed no effect on mortality (5, 10). A recent 3-country trial in which women took 60 000 μg RE (200 000 IU) vitamin A postpartum and their infants were given 7000 μg RE (25 000 IU) vitamin A with each of 3 diphtheria-pertussis-tetanus immunizations in the first 4 mo of life similarly found no improvement in infant survival (11). These findings conflict with those of a trial in Indonesia, where infant mortality was markedly reduced after newborns were given 15 000 μg RE (50 000 IU) vitamin A (9). With this notable exception, the balance of evidence to date suggests that the predominant causes of death in infants <6 mo of age are unresponsive to changes in maternal or infant vitamin A status.

In summary, although routine maternal supplementation with vitamin A or β-carotene had a large effect on pregnancy-related mortality through 12 wk postpartum (13) and on night blindness during and after pregnancy (20), there was no discernable effect on fetal loss or infant mortality through 6 mo of age. Improved vitamin A or β-carotene intake may be important for improving maternal survival in vitamin A–deficient populations, but the weekly doses provided in this trial are unlikely to affect the survival of offspring through the first half of infancy. This lack of effect contrasts with the consistent and sizable reductions in infant and child mortality observed with vitamin A supplementation after the first 6 mo of life (1–8).

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