

Double blind, cluster randomised trial of low dose supplementation with vitamin A or β carotene on mortality related to pregnancy in Nepal

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Editorial by Olsen

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Abstract

Objective To assess the impact on mortality related to pregnancy of supplementing women of reproductive age each week with a recommended dietary allowance of vitamin A, either preformed or as β carotene.

Design Double blind, cluster randomised, placebo controlled field trial.

Setting Rural southeast central plains of Nepal (Sarlahi district).

Subjects 44 646 married women, of whom 20 119 became pregnant 22 189 times.

Intervention 270 wards randomised to 3 groups of 90 each for women to receive weekly a single oral supplement of placebo, vitamin A (7000 μ g retinol equivalents) or β carotene (42 mg, or 7000 μ g retinol equivalents) for over 3½ years.

Main outcome measures All cause mortality in women during pregnancy up to 12 weeks post partum (pregnancy related mortality) and mortality during pregnancy to 6 weeks postpartum, excluding deaths apparently related to injury (maternal mortality).

Results Mortality related to pregnancy in the placebo, vitamin A, and β carotene groups was 704, 426, and 361 deaths per 100 000 pregnancies, yielding relative risks (95% confidence intervals) of 0.60 (0.37 to 0.97) and 0.51 (0.30 to 0.86). This represented reductions of 40% ($P < 0.04$) and 49% ($P < 0.01$) among those who received vitamin A and β carotene. Combined, vitamin A or β carotene lowered mortality by 44% (0.56 (0.37 to 0.84), $P < 0.005$) and reduced the maternal mortality ratio from 645 to 385 deaths per 100 000 live births, or by 40% ($P < 0.02$). Differences in cause of death could not be reliably distinguished between supplemented and placebo groups.

Conclusion Supplementation of women with either vitamin A or β carotene at recommended dietary amounts during childbearing years can lower mortality related to pregnancy in rural, undernourished populations of south Asia.

Introduction

Vitamin A deficiency is common among women in developing countries. Mean serum retinol concentrations of about 1.05 μ mol/l (300 μ g/l) have been reported during pregnancy among diverse groups of south Asian women¹⁻⁶ in comparison with values of 1.57-1.75 μ mol/l (450-500 μ g/l) in better nourished populations.⁷

Concern about maternal vitamin A deficiency has focused on its effects on fetal and infant vitamin A status,^{1 8-10} health, and survival,^{8 11} with little attention being paid to its effects on the health consequences for the woman. An early trial in England reported that maternal vitamin A supplementation in late pregnancy through the first week post partum could reduce the incidence of puerperal sepsis,¹² but this lead was ignored. In Nepal maternal night blindness, an indicator of vitamin A deficiency,¹³ has been associated with increased risks of urinary or reproductive tract infections and diarrhoea or dysentery¹⁴ and raised acute phase protein concentrations during infection.¹⁵ That vitamin A deficiency could predispose women to increased infectious morbidity and mortality is supported by evidence in children and animals.⁸ Mechanisms underlying such an effect could include impaired barrier defences of epithelial tissues and compromised innate and acquired immunity.^{8 16}

We conducted a study in rural Nepal to assess whether routine supplementation of women with normal, dietary amounts of vitamin A or provitamin A β carotene could favourably affect fetal, infant, or maternal health and survival. In this paper we examine the effects of supplementation on maternal all cause mortality.

Participants and methods

Protocol

The study was a double blind, placebo controlled, cluster randomised trial carried out in Sarlahi district, in the southern plains of Nepal, to assess the effects of continuous, weekly, low dose supplementation of vitamin A or provitamin A β carotene on mortality related to pregnancy in women of reproductive age.

The trial required that the two supplementation groups (vitamin A or β carotene) enrol a combined total of around 14 000 pregnancies (roughly 7000 in each group) and the placebo group around 7000 pregnancies, yielding an assignment ratio of 2 to 1, to show a $\geq 40\%$ reduction in mortality related to pregnancy with $\geq 80\%$ power ($1 - \beta$) and 95% confidence ($1 - \alpha$). These assumptions were based on an estimated mortality from pregnancy of > 600 deaths per 100 000 pregnancies in the study area. Smaller differences ($\geq 20\%$) in fetal and infant mortality up to 6 months of age would be discernible with the same sample size.

A total of 270 wards in 30 subdistricts (9 wards each) covering an area of around 500 sq km with a total population of around 176 000 participated in the study. At a local crude birth rate of 41 per 1000 population per year, we anticipated that recruiting 21 000 pregnancies would take around 3 years. The purpose of the trial was explained at community meetings, and written consent to participate was obtained from subdistrict leaders during the year before the start of the trial. Women of childbearing age who were married and living with their husbands as of the first week of March 1994 were recruited to the trial after giving their verbal consent. Newly married women were recruited throughout the trial. Women who were already married who had moved into study wards were not eligible to participate to minimise crossover.

All wards were assigned in Kathmandu by a random draw of numbered chits, blocked on subdistrict, for eligible women to receive one of three identical coded supplements. These were opaque, gelatinous capsules containing peanut oil and 23 300 IU of preformed vitamin A (7000 μg retinol equivalents) as retinyl palmitate, 42 mg of all *trans* β carotene (7000 μg retinol equivalents, assuming a conversion ratio to retinol of 6 to 1 after uptake¹⁷), or no vitamin A or β carotene (placebo) (fig 1). The dosage was intended to deliver an approximate recommended dietary allowance during pregnancy and lactation¹⁷ on a weekly basis. All capsules also contained about 5 mg dl- α -tocopherol as an antioxidant.

Field procedures

From April 1994 to September 1997 a staff of 432 local female workers carried out weekly home visits and dosed participating women with their assigned supplement. At least 4 days between doses were maintained to avoid any potential risk of toxicity from receiving supplements on two consecutive days. Workers recorded the survival of the women, receipt of capsules, menstrual activity in the previous week, and pregnancy status as reported by women. They revisited the homes of women who were absent until they were able to give them the dose or until the last day of a dosing week. Capsules were not left at homes.

Five months after supplementation and reporting were running smoothly, newly enrolled pregnant women entered into a protocol that included a mid-pregnancy, home based, 7 day dietary, morbidity, and activity assessment and measurement of arm circumference by one of a trained team of about 30 interviewers. Severely ill women were referred to one of seven local health centres for evaluation. A second visit during the third trimester included socioeconomic evaluation. Seven months after the start of the study

newly enrolled pregnant women from a subsample of three contiguous subdistricts (27 wards), selected for access, were enrolled for additional measures that required blood collection and measurement of concentrations of retinol and β carotene.

A history of events and illnesses preceding death was obtained by interviewing family members of the dead woman (so called verbal autopsy), usually within one month after the death had been reported. These data were reviewed and a "proximate" cause of death assigned by two doctors (SKK and SMD), one of whom was an obstetrician-gynaecologist; both were blind to treatment allocation. Differences in assignment were discussed until the reviewers agreed on a cause of death.

Analysis

Comparability of randomised groups by socioeconomic and dietary characteristics of women during their first enrolled pregnancy was assessed by the χ^2 test; differences in distributions of serum retinol and β carotene concentrations were tested by analysis of variance and comparing the two groups with the *t* test. We checked compliance in each supplement group by examining the percentage of all eligible doses during the trial (or until death) taken by women and the differences in serum retinol and β carotene concentrations by code among pregnant women in the substudy sample.

Ascertained pregnancies served as the denominator for rate estimation, of which around 91% ended in one or more live births and 6-7% as a declared miscarriage or stillbirth in each group. The remaining 2% of pregnancies had been reported by women at six or more weekly visits but had no reported outcome. We considered these pregnancies to have ended in loss. Pregnancies declared for shorter periods for which no outcome was recorded were considered false positive reports and excluded from the analysis. Eligible pregnancies for this mortality analysis were those ending from mid-July 1994 (by which time women had been routinely given supplements for ≥ 5 months) and the end of June 1997, which permitted 12 weeks of postpartum dosing and follow up.

Mortality was evaluated on an intention to treat basis—that is, by supplement assignment irrespective of compliance. Mortality related to pregnancy and specific causes for each group was calculated from deaths that occurred during pregnancy up to 12 weeks post partum and was expressed per 100 000 pregnancies. We extended postpartum follow up from 6 to 12 weeks because maternal mortality related to malnutrition could extend beyond the conventional period of 6 weeks. However, we also examined impact on the maternal mortality ratio (for which we excluded deaths due to reported injury and all deaths > 6 weeks post partum) in relation to live births. Relative risks with 95% confidence intervals were calculated with the placebo group as the reference.¹⁸ Each confidence interval was adjusted to account for the fact that the ward rather than the person was the unit of randomisation. A quasi-likelihood Poisson regression model was used to estimate the degree of overdispersion in the ward specific death rates.^{19, 20} This overdispersion, due to the design effect, of about 21% of the variance resulted in a 10% inflation in the length of a confidence interval which was applied to the natural logarithm of all estimates of relative risk.

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Ethical review

The trial protocol was reviewed and approved by the Nepal Health Research Council in Kathmandu, the

Joint Committee on Clinical Investigation at the Johns Hopkins School of Medicine, and the Teratology Society in Bethesda. Two data and safety monitoring committees approved the trial, one in Baltimore and the other in Kathmandu.

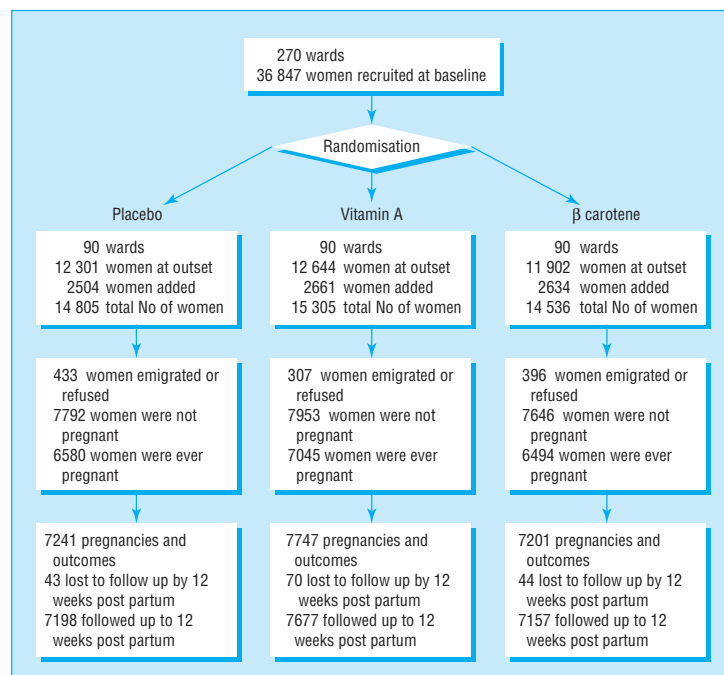


Fig 1 Study design with details of follow up

Table 1 Characteristics of mothers during their first study pregnancy by supplement group. Values are numbers (percentages) unless stated otherwise

Characteristic	Placebo	Vitamin A	β carotene
Age			
No of women	5249	5685	5266
<20	1176 (22.4)	1268 (22.3)	1227 (23.3)
20-29	3249 (61.9)	3456 (60.8)	3081 (58.5)
≥30	824 (15.7)	961 (16.9)	958 (18.2)
Arm circumference			
No of women	4639	5053	4663
<21.5 cm	2538 (54.7)	2759 (54.6)	2513 (53.9)
Diet			
No of women	4702	5094	4704
More than once in previous 7 days†:			
Meat/fish/egg	1278 (27.2)	1365 (26.8)	1246 (26.5)
Dairy products	2383 (50.7)	2536 (49.8)	2439 (51.9)
Yellow fruits/vegetables	738 (15.7)	810 (15.9)	790 (16.8)
Dark green leaves	1752 (37.3)	1858 (36.5)	1803 (38.4)‡
Substance use			
No of women	4702	5094	4704
In previous 7 days:			
Smoked cigarettes	1307 (27.8)	1370 (26.9)	1397 (29.7)*
Drank alcohol	385 (8.2)	366 (7.2)	498 (10.6)**
Socioeconomic status¶			
No of women	5017	5448	5036
Literate	797 (15.9)	714 (13.1)	821 (16.3)**
Owned radios	1415 (28.2)	1471 (27.0)	1455 (28.9)
Caste:			
No of women	4773	5179	4754
Low caste or not Hindu	826 (17.3)	1274 (24.6)	979 (20.6)**
Delivery:			
No of women	4784	5196	4813
Delivered at health facility	139 (2.9)	151 (2.9)	140 (2.9)

*P<0.01, **P<0.001 by χ^2 test (df=2).

†At first home interview during mid-trimester.

‡Data were missing on consumption of dark green leaves for eight women in β carotene group.

¶At home interview during late third trimester.

Results

A total of 44 646 women were recruited, 36 847 at the outset and 7799 newly married women during the trial (fig 1). In all, 1136 (2.5%) women were excluded because they emigrated before becoming pregnant or dying or because they declined to be recruited. Overall, 20 119 (45%) women were pregnant 22 189 times. Maternal survival was known after all pregnancy outcomes, but 157 women were lost to follow up during the postpartum period (their median follow up time post partum was around 2 weeks in each group). As the women lost to follow up had completed pregnancies they were included in the denominators for estimating mortality.

At the time of their first study pregnancy, the three groups of women were comparable in age, arm circumference, and weekly dietary intakes. Small differences were evident with respect to cigarette smoking, alcohol consumption, and literacy. A smaller percentage of the placebo group were of low Hindu caste or were not Hindus. Only 3% of pregnancies were delivered at a health post, clinic, or hospital (table 1).

Women who were pregnant more than once during the trial received a greater percentage of their total eligible supplements than those who were never pregnant (fig 2). For example, half of the women who were ever pregnant and 44% of those who were never pregnant received ≥80% of their intended supplements. Over 75% of the pregnant women received at least half of their eligible doses—that is, more than half of a dietary allowance for those receiving vitamin A or β carotene—compared with around 62% of those who were never pregnant. Compliance was about 3% lower in the β carotene group in the mid-range of supplement intake.

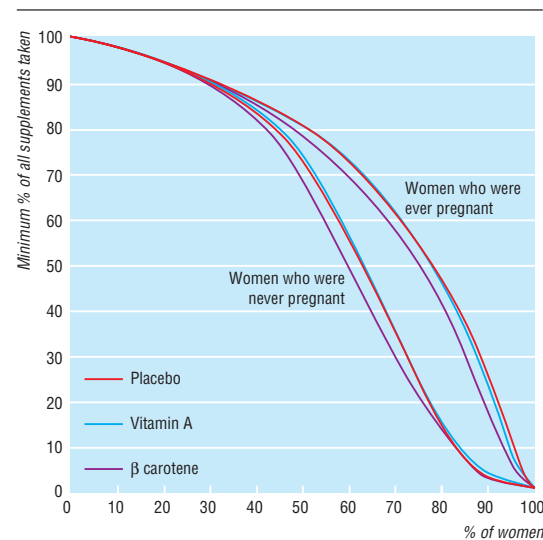


Fig 2 Minimum percentages of all eligible weekly supplements (to the end of the trial or death) taken by percentages of women who were ever or never pregnant during the trial by supplement group

Among 1446 women who had their first pregnancy in the 27 substudy wards between September 1994 and July 1996, 1025 (71%) were seen at the clinic, of whom 978 (95%) were confirmed pregnant by urine test. From these women, serum samples were available for 935 (96%) and 916 (94%) mid-pregnancy determinations of retinol and β carotene concentrations, respectively. The mean serum retinol concentration was lowest in the placebo group (1.02 $\mu\text{mol/l}$), highest among vitamin A recipients (1.30 $\mu\text{mol/l}$), and between these two values in the β carotene group (1.14 $\mu\text{mol/l}$) (table 2). The percentage of women by supplement group with serum retinol concentrations $<0.70 \mu\text{mol/l}$ followed the same pattern. The mean β carotene concentration was significantly higher (0.20 $\mu\text{mol/l}$) and the percentage of women with concentrations $<0.09 \mu\text{mol/l}$ lower (26.5%) in the β carotene than in the vitamin A and placebo groups (around 0.14 $\mu\text{mol/l}$ and about 42% in both groups). Thus, compliance with taking supplements seems to have been adequate to change biochemical variables.

Mortality related to pregnancy up to 12 weeks post partum was 704, 426, and 361 maternal deaths per 100 000 pregnancies in the placebo, vitamin A, and β carotene groups, yielding relative risks of 0.60 (0.37 to 0.97) ($P=0.04$) and 0.51 (0.30 to 0.86) ($P=0.01$) in the vitamin A and β carotene groups, respectively (table 3). Mortality among women receiving β carotene was not significantly different from that in the vitamin A group (relative risk 0.85 (0.48 to 1.49), $P=0.57$). We therefore combined the effects to obtain a relative risk of 0.56 (0.37 to 0.84), reflecting a 44% reduction in mortality related to pregnancy associated with vitamin A or β carotene supplementation ($P=0.005$). This survival effect was evident after 1½ years of the trial, reflected by a relative risk of 0.54 (0.32 to 0.90) ($P=0.02$), which remained stable during the last part of the trial (relative risk 0.61 (0.31 to 1.19), $P=0.15$, data not shown). The relative risk was protective for both nutritional supplements during pregnancy, from the end of pregnancy to 6 weeks post partum, and from 6 to 12 weeks post partum (table 4).

Analysis of cause specific mortality, based on interviews with relatives, showed protective but non-significant effects of supplementation against risk of death from obstetric causes and infection (table 5).

Table 2 Serum retinol and β carotene concentrations in women during mid-pregnancy

	Placebo	Vitamin A	β carotene
Retinol ($\mu\text{mol/l}$)			
No of women	265	314	356
Mean (SD)*	1.02 (0.35)	1.30 (0.33)	1.14 (0.39)
No (%) $<0.70 \mu\text{mol/l}^\dagger$	51 (19)	9 (3)	48 (14)
β carotene ($\mu\text{mol/l}$)			
No of women	261	308	347
Mean (SD)‡	0.14 (0.12)	0.15 (0.14)	0.20 (0.17)
No (%) $<0.09 \mu\text{mol/l}^\ddagger$	112 (43)	130 (42)	92 (27)

* $P<0.0001$ by analysis of variance; $P\leq 0.002$ for all comparisons by t test.
 $^\dagger P<0.0001$ by χ^2 test ($df=2$); $P<0.0001$ for vitamin A v placebo and vitamin A v β carotene, and $P=0.052$ for vitamin A v β carotene by χ^2 test (all $df=1$).
 $^\ddagger P<0.0001$ by analysis of variance; $P<0.0001$ for β carotene v placebo and β carotene v vitamin A, and $P=0.23$ for vitamin A v placebo by t test.
 $^\S P<0.0001$ by χ^2 test ($df=2$); $P<0.0001$ for β carotene v placebo and β carotene v vitamin A, and $P>0.87$ for vitamin A v placebo by χ^2 test ($df=1$).

Table 3 Impact of supplementation on mortality related to pregnancy up to 12 weeks post partum

	Placebo	Vitamin A	β carotene	Vitamin A or β carotene
No of pregnancies*	7241	7747	7201	14 948
No of deaths	51	33	26	59
Mortality (per 100 000 pregnancies)	704	426	361	395
Relative risk (95% CI)	1.00	0.60 (0.37 to 0.97)	0.51 (0.30 to 0.86)	0.56 (0.37 to 0.84)
P value		<0.04	<0.01	<0.005

*Includes 157 pregnancies that were lost to follow up (43, 70, and 44 in placebo, vitamin A, and β carotene groups respectively).

Point estimates of relative risk are stronger for β carotene than for vitamin A. Supplementation was associated with protection from death attributed to injuries and other miscellaneous causes.

The maternal mortality ratio was 645 (42 deaths/6670 live births), 407 (29/7074), and 361 (23/6643) per 100 000 live births in the placebo, vitamin A, and β carotene groups, respectively ($P=0.08$ for vitamin A and 0.04 for β carotene v placebo). The ratio for women receiving either vitamin A or β carotene was 385, yielding a relative risk of 0.60 (0.39 to 0.93), representing a 40% reduction in mortality by this measure ($P=0.02$).

Discussion

In this poor, rural Asian setting the risk of death related to pregnancy was lowered, by about 40%, among

Table 4 Impact of supplementation on mortality in women during and after pregnancy

	Placebo	Vitamin A	β carotene	Vitamin A or β carotene
No of pregnancies*	7241	7747	7201	14 948
During pregnancy				
No of deaths	17	11	8	19
Mortality (per 100 000 pregnancies)	235	142	111	127
Relative risk (95% CI)	1.00	0.60 (0.26 to 1.38)	0.47 (0.18 to 1.20)	0.54 (0.26 to 1.11)
P value		0.23	0.11	0.10
0-6 weeks post partum				
No of deaths	26	18	16	34
Mortality (per 100 000 pregnancies)	359	232	222	227
Relative risk (95% CI)	1.00	0.65 (0.34 to 1.25)	0.62 (0.31 to 1.23)	0.63 (0.36 to 1.11)
P value		0.20	0.17	0.11
7-12 weeks post partum				
No of deaths	8	4	2	6
Mortality (per 100 000 pregnancies)	110	52	28	40
Relative risk (95% CI)	1.00	0.47 (0.13 to 1.76)	0.25 (0.04 to 1.42)	0.36 (0.11 to 1.14)
P value		0.26	0.12	0.08

*Includes 157 pregnancies that were lost to follow up (43, 70, and 44 in placebo, vitamin A, and β carotene groups respectively).

Table 5 Impact of supplementation on cause related mortality in women during pregnancy up to 12 weeks post partum. Values are numbers of women unless stated otherwise

Cause	Placebo (n=7241)	Vitamin A (n=7747)	β carotene (n=7201)	Vitamin A or β carotene (n=14 948)
Obstetric				
Haemorrhage*	5	4	4	8
Eclampsia	6	4	2	6
Other†	7	9	4	13
Total	18	17	10	27
Mortality (per 100 000 pregnancies)	249	219	139	181
Relative risk (95% CI)	1.00	0.88 (0.42 to 1.81)	0.56 (0.24 to 1.31)	0.73 (0.38 to 1.41)
Infection				
Gastroenteritis	4	2	3	5
Sepsis	5	5	2	7
Respiratory infection	1	5	1	6
Other‡	5	3	3	6
Total	15	15	9	24
Mortality (per 100 000 pregnancies)	207	194	125	161
Relative risk (95% CI)	1.00	0.94 (0.42 to 2.05)	0.60 (0.24 to 1.51)	0.78 (0.39 to 1.58)
Related to injury¶				
Total	5	0	1	1
Mortality (per 100 000 pregnancies)	69	0	14	7
Relative risk (95% CI)	1.00	0	0.20 (0.02 to 2.32)	0.10 (0.01 to 1.14)
Miscellaneous				
Chronic illness§	3	0	2	2
Uncertain	6	2	0	2
No information	4	0	3	3
Total	13	2	5	7
Mortality (per 100 000 pregnancies)	180	26	69	47
Relative risk (95% CI)	1.00	0.14 (0.03 to 0.76)	0.38 (0.13 to 1.21)	0.26 (0.09 to 0.73)

*Includes antepartum and postpartum haemorrhage and retained placenta.

†Includes obstetric shock, postpartum shock, and obstructed labour.

‡Includes typhoid fever, tetanus, hepatitis, and leishmaniasis.

¶Includes burns, drowning, snakebite, and hanging.

§Includes anaemia, asthma, and leukaemia.

women who were routinely given dietary supplements of vitamin A or β carotene rather than placebo. Effect estimates were similar during pregnancy and post partum. The protective impact was established after 1½ years of supplementation, reflecting consistency of the effect over time and a potential duration of dosing a population by which a clear mortality reduction could be expected. The impact on mortality was similar when expressed as a maternal mortality ratio that excluded deaths related to injury and those occurring more than 6 weeks post partum. The comparability of groups of pregnant women with respect to compliance and demographic, socioeconomic, dietary, and obstetric variables shows that the observed survival effect was unlikely to have resulted from imbalances in other factors that could have influenced maternal mortality.

We intended the weekly dosage of vitamin A or β carotene to deliver the equivalent of a liberal dietary allowance of vitamin A for pregnant or lactating women.¹⁷⁻²¹ Although more than three quarters of all women who became pregnant during the trial received at least half of their recommended allowance of vitamin A through supplements, only half took 80% or more of their eligible supplements. This suggests that the risk of maternal death in populations who are deficient in vitamin A could be substantially lowered with modest increases in vitamin A or β carotene intake, as has been shown in children.²²

The interview with relatives was a feasible and insightful way to investigate causes of death in a population where medical diagnoses were unobtainable; however, this method may be subject to considerable

imprecision and misclassification,²³⁻²⁴ particularly given the complex nature of deaths related to pregnancy and the common lack of pathognomonic signs or symptoms that would be evident to lay relatives. Our interviews with relatives suggested there was a 22% reduction in infectious causes of death $((1 - 0.78) \times 100)$, but the finding was inconclusive. Some deaths due to infection may have been misclassified as uncertain. Eight of the 12 deaths with completed interviews (five women had been in the placebo group and three in the vitamin A and β carotene group) had reported symptoms that were consistent with infectious disease before death.

A 27% decrease in maternal mortality was attributed to obstetric causes in women receiving supplements. The effect seemed to be more strongly associated with β carotene (relative risk 0.56, $P = 0.18$) than vitamin A (relative risk 0.88, $P = 0.73$). Although the putative role of antioxidant defences in preventing disease²⁵ and an in vivo antioxidant role for β carotene²⁶ remain controversial, β carotene, acting as an antioxidant,²⁷⁻²⁸ could have reduced some forms of obstetric risk in this malnourished population. Low serum β carotene concentrations have been observed in pregnant Asian² and African²⁹ women with pre-eclampsia and eclampsia, whose pathogenesis entails vascular endothelial injury that may be associated with oxidative stress.³⁰⁻³¹ Placental abruption has also been associated with depressed serum antioxidant concentrations, including β carotene.³²

Currently, supplementation programmes of weekly low doses of vitamin A or β carotene do not exist for

Key messages

- Maternal vitamin A deficiency, evident as night blindness or low serum retinol concentration during pregnancy, is widely prevalent in rural south Asia
- In Nepal, women of reproductive age who were given 7000 µg retinol equivalents of vitamin A on a weekly basis showed a reduction in mortality related to pregnancy of 40%
- Weekly dosing with 42 mg β carotene (also providing 7000 µg retinol equivalents) lowered their mortality by 49%
- Preventing maternal vitamin A deficiency in rural South Asia can lower the risk of mortality of women during and after pregnancy

women of reproductive age, although this approach may be a cost effective way of preventing iron deficiency anaemia in the developing world.³³ Our findings suggest that raising the intake of preformed vitamin A or provitamin A carotenoids towards the values recommended for pregnancy or lactation, presumably by supplementation or by dietary means, can complement antenatal and essential obstetric services in lowering maternal mortality in rural south Asia.

The NNIPS-2 (Nepal Nutrition Intervention Project-Sarlahi) Study Group includes (in addition to the authors) Drs Ramesh Adhikari, Bhakta Raj Dahal, Michele Dreyfuss, Rebecca Stoltzfus, James Tielsch, and Sedigheh Yamini-Roodsari; Noor Nath Acharya, Dev N Mandal, Kerry Schulze, Tirtha R Shaky, Lee Shu-Fune Wu, Andre Hackman, and Gwendolyn Clemens. We thank Drs Frances Davidson, Victor Barbiero, Tim Quick, Martin Frigg, James Tonascia, Frederick Trowbridge, Calvin Willhite, and David Calder; Molly Gingerich, Charles Llewellyn, David Peat, Lisa Gautschi, Ravi Ram, and more than 550 staff of the NNIPS-2 study for their help.

Contributors: KPW was the principal investigator, formulated the major hypotheses, directed the study and analysis, wrote the paper, and is guarantor for the study. JK helped in study design, developed the data management and quality control systems, analysed the data, and contributed to writing the paper. SKK helped design forms and develop procedures and assigned causes of maternal death based on review and interpretation of verbal autopsies. SLC developed field procedures, helped in designing forms, supervised field supplementation and data collection, and helped to edit the paper. EKP helped design and pretest forms, managed data editing and entry and quality control systems and participated in data analysis and interpretation of findings. SRS supervised field data collection and supplementation and helped prepare manuals of field operations. PBC designed the data management and quality control systems. SMD helped develop protocols for assessing maternal morbidity and for verbal autopsies. PC helped in implementing the field study and contributed to the data analysis, interpretation of findings, and preparation of the manuscript. RPK oversaw the implementation and integration of the trial in the community. AS had the original idea of a maternal supplementation trial, helped in its conceptualisation, reviewed its design and procedures, and contributed to writing the paper.

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