Effect of vitamin A supplementation in women of reproductive age on maternal survival in Ghana (ObaapaVitA): a cluster-randomised, placebo-controlled trial

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Summary

Background A previous trial in Nepal showed that supplementation with vitamin A or its precursor (betacarotene) in women of reproductive age reduced pregnancy-related mortality by 44% (95% CI 16–63). We assessed the effect of vitamin A supplementation in women in Ghana.

Methods ObaapaVitA was a cluster-randomised, double-blind, placebo-controlled trial undertaken in seven districts in Brong Ahafo Region in Ghana. The trial area was divided into 1086 small geographical clusters of compounds with fieldwork areas consisting of four contiguous clusters. All women of reproductive age (15–45 years) who gave informed consent and who planned to remain in the area for at least 3 months were recruited. Participants were randomly assigned by cluster of residence to receive a vitamin A supplement (25 000 IU retinol equivalents) or placebo capsule orally once every week. Randomisation was blocked and based on an independent, computer-generated list of numbers, with two clusters in each fieldwork area allocated to vitamin A supplementation and two to placebo. Capsules were distributed during home visits undertaken every 4 weeks, when data were gathered on pregnancies, births, and deaths. Primary outcomes were pregnancy-related mortality and all-cause female mortality. Cause of death was established by verbal post mortems. Analysis was by intention to treat (ITT) with random-effects regression to account for the cluster-randomised design. Adverse events were synonymous with the trial outcomes. This trial is registered with ClinicalTrials.gov, number NCT00211341.

Findings 544 clusters (104 484 women) were randomly assigned to vitamin A supplementation and 542 clusters (103 297 women) were assigned to placebo. The main reason for participant drop out was migration out of the study area. In the ITT analysis, there were 39 601 pregnancies and 138 pregnancy-related deaths in the vitamin A supplementation group (348 deaths per 100 000 pregnancies) compared with 39 234 pregnancies and 148 pregnancy-related deaths in the placebo group (377 per 100 000 pregnancies); adjusted odds ratio 0·92, 95% CI 0·73–1·17; p=0·51. 1326 women died in 292 560 woman-years in the vitamin A supplementation group (453 deaths per 100 000 years) compared with 1298 deaths in 289 310 woman-years in the placebo group (449 per 100 000 years); adjusted rate ratio 1·01, 0·93–1·09; p=0·85.

Interpretation The body of evidence, although limited, does not support inclusion of vitamin A supplementation for women in either safe motherhood or child survival strategies.

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Introduction

Vitamin A deficiency is a well-recognised nutritional problem,[1,2] and the leading cause of preventable childhood blindness.[3] In the 1990s, vitamin A supplementation became a key child survival intervention[4,5] after a series of eight trials[6–13] showed a pooled reduction in mortality of 23% (95% CI 16–38) in children aged between 6 months and 5 years who were given the intervention compared with those given placebo.[2–14]

Findings from a randomised controlled trial in Nepal suggested that vitamin A supplementation might have a similar role in preventing maternal deaths; provision of supplements of vitamin A or its precursor (betacarotene) to women of reproductive age reduced pregnancy-related mortality by 44% (95% CI 16–63; p<0·005).[15] If this reduction represents a real effect, then low-dose vitamin A supplementation could become an important safe motherhood intervention. Vitamin A supplementation is safe (including during pregnancy), inexpensive, and potentially deliverable at community level, even in the absence of strong health systems advocated in existing safe motherhood strategies.[16,17]

However, changing policy without testing vitamin A supplementation in trials in other settings was deemed premature. Other evidence of the effect of vitamin A supplementation comes from two trials in which only pregnant women received supplements (table 1). Provisional results from the trial in Bangladesh suggested no effect of vitamin A supplementation on pregnancy-related mortality (relative risk 1·15, 95% CI 0·78–1·81).[18] The trial in Indonesia compared a daily multiple micronutrient supplement containing vitamin A with a

supplement consisting of just iron and folic acid; pregnancy-related mortality rates were similar in the two groups (relative risk 1·03, 95% CI 0·64–1·68).[19]

The ObaapaVitA trial assessed the effects of giving vitamin A supplementation to all women of reproductive age in an African setting, where maternal mortality ratios are among the highest in the world.[20] The trial attempted to replicate the findings of the Nepal trial by giving supplements to all women of reproductive age.

Methods

Participants

The main objective of the ObaapaVitA trial was to assess the effect of weekly, low-dose vitamin A supplementation in women of reproductive age on pregnancy-related mortality and all-cause female mortality. Secondary objectives were to assess the effects of vitamin A supplementation on maternal morbidity and perinatal and infant mortality, and to explore effects on cause-specific pregnancy-related mortality by meta-analysis with other trials.

All women aged 15–45 years living in seven predominantly rural districts in Brong Ahafo Region in Ghana, who were capable of giving informed consent and who planned to live in the trial area for at least 3 months were eligible for enrolment. Implementation was phased by district; fieldworkers visited all compounds over a 4–8 week period and explained the trial by reading from a standard information sheet in Twi (the most commonly spoken language), by use of an interpreter if necessary. Women were given the opportunity to ask questions and, if they provided consent, asked to sign the enrolment form or make a thumbprint. Enrolment continued throughout the trial; fieldworkers recruited eligible women who migrated into their areas and girls who reached 15 years of age. Once recruited, women continued in the trial even beyond 45 years of age.

Capsule distribution started in Kintampo North and Kintampo South in December, 2000, in Wenchi and Tain in June, 2001, in Techiman in June, 2002, and in Nkoranza North and Nkoranza South in January, 2003. Distribution ended in September, 2008, with data collection continuing until the end of October, 2008.

The trial was approved by the ethics committees of the Ghana Health Service and the London School of Hygiene and Tropical Medicine. Full informed consent (by signature or thumbprint) was obtained from all trial participants; a substudy explored their understanding of the trial.[21]

Procedures

Women were randomly assigned, according to their cluster of residence, to receive a vitamin capsule or placebo capsule orally once every week. The vitamin A capsule consisted of 25 000 IU (7500 µg) retinol equivalents in soybean oil in a dark red opaque soft gel. The placebo capsule consisted of soybean oil only. The dose of vitamin A was selected to deliver the recommended dietary allowance while being safe during pregnancy.[22,23] The capsules were manufactured by Accucaps Industries (Windsor, ON, Canada); Roche (Basel, Switzerland) donated vitamin A palmitate. Women were visited at home every 4 weeks, and given four capsules to be taken over the next 4 weeks; capsules were kept in vials, with cotton wool to absorb humidity in the rainy season.

There was no direct observation of capsule taking during home visits. Instead, adherence was supported by an extensive Information, Education, and Communication (IEC) programme, based on formative research undertaken before the trial began[24] with women encouraged to take their capsules on the same day, Sunday, to foster social support and reduce forgetfulness. The IEC strategy also included reminder announcements on the radio and in the community (by means of loudspeaker vans and drum beaters), churches, and mosques; radio discussion programmes and community meetings to introduce the trial and answer questions; posters in all compounds; a book of frequently asked questions with answers for traditional healers, traditional birth attendants, drug sellers, and health workers in the trial area as well as fieldworkers; and a message of the month for fieldworkers to give women. A specially trained IEC team addressed any adherence issues through fieldworker reports and regular focus groups with community members, and identified possible solutions.

For the **full protocol for this study** see http://www.lshtm.ac.uk/nphiru/research/obaapavita/Obaapa_Trial_Protocol.pdf

Randomisation and masking

The trial area was divided into clusters of compounds, with fieldworkers responsible for a fieldwork area of four contiguous clusters, visiting women in one cluster per week over a 4-weekly cycle; clusters were designed

	Country	Supplement tested	Approximate number of pregnancies per group	Deaths per 100 000 pregnancies in control group
All women of reproductive age				
NNIPS-2[15]	Nepal	Vitamin A supplementation once every week (23 333 IU RE)	7000	704
NNIPS-2[15]	Nepal	Betacarotene once every week (23 333 IU RE)	7000	704
ObaapaVitA	Ghana	Vitamin A supplementation once every week (25 000 IU RE)	39 000	377
Pregnant women				
JiVitA-1[18]	Bangladesh	Vitamin A supplementation once every week (23 333 IU RE)	20 000	209
JiVitA-1[18]	Bangladesh	Betacarotene once every week (23 333 IU RE)	20 000	209
SUMMIT[19]	Indonesia	Daily multiple micronutrients (including 2667 IU RE)	7000	278

NNIPS-2=Nepal Nutrition Intervention Project Sarlahi 2. RE=retinol equivalents. SUMMIT=Supplementation with Multiple Micronutrients Intervention Trial.

Table 1: **Trials assessing the effect of vitamin A supplementation on maternal mortality, by target group**

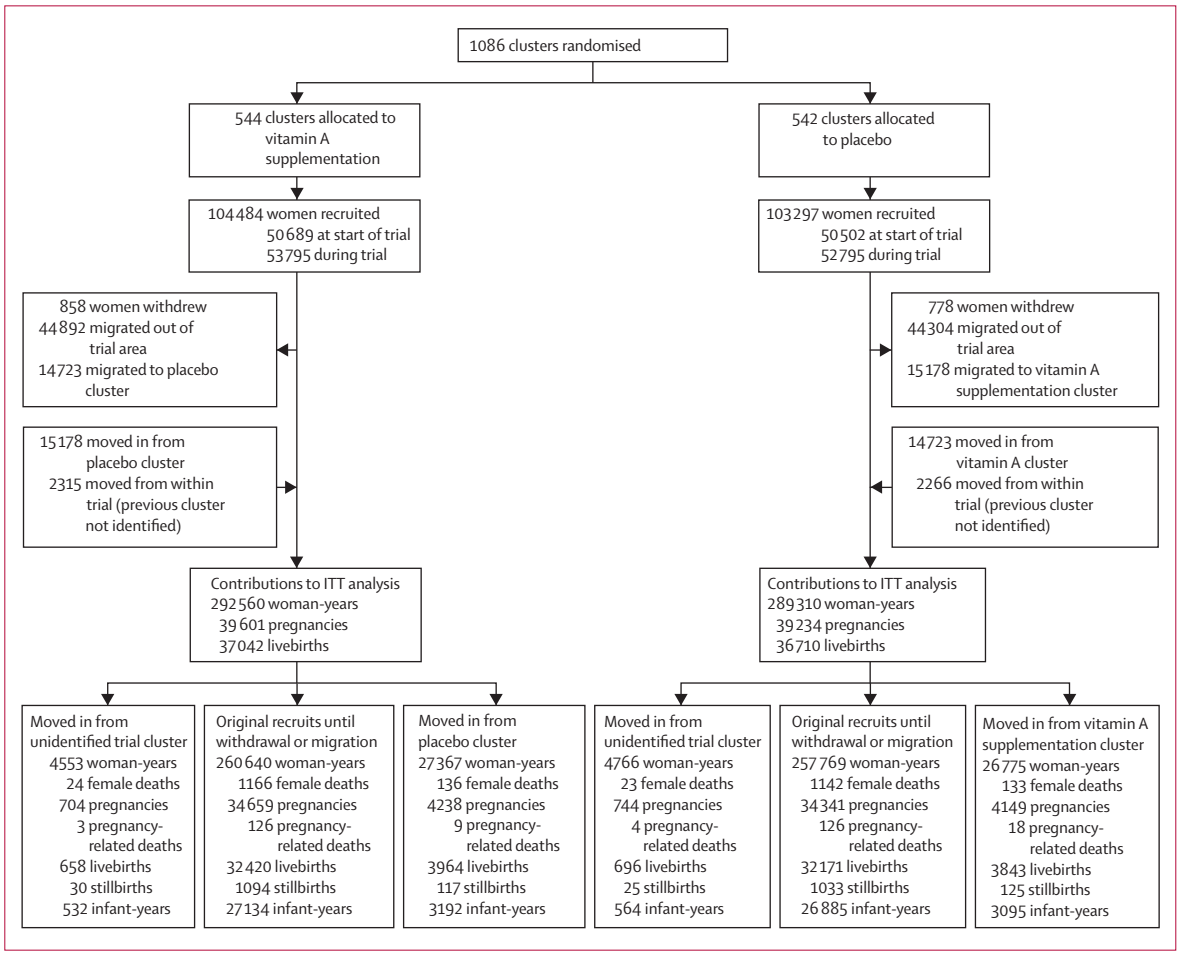

Figure 1: **Trial profile**
Intention-to-treat (ITT) analysis excludes first 6 months after recruitment. See Methods section for details.

to contain an initial maximum of 120 enrolled women. A computer-generated randomisation list was prepared for the capsule manufacturers by an independent statistician on the data monitoring and ethics committee. The capsules were packaged in labelled jars, for each cluster for each week of the trial. Trial personnel had no access to the randomisation list or to any information that would allow them to deduce or change the cluster allocation.

Randomisation was by cluster to keep the possibility of women receiving the wrong capsules to a minimum; fieldworkers only ever had one jar in their possession, which contained the capsules to be given to women they were visiting that week. All women in a compound received the same capsules to avoid any allocation errors should their vials accidentally get mixed up. Randomisation was blocked with two clusters in each fieldwork area allocated to vitamin A supplementation and two clusters allocated to placebo to ensure geographical matching of intervention and control groups. Two fieldwork areas contained three rather than four clusters; their randomisation was undertaken in exactly the same way but the allocation of the fourth cluster was ignored.

All participants and trial personnel (including those distributing capsules and collecting, processing, and analysing data) were masked to treatment assignment for the duration of the trial. Placebo capsules were identical in taste and appearance to the vitamin A capsules.

Data collection

At home visits undertaken every 4 weeks, fieldworkers gathered data for pregnancies, births, deaths, migrations, hospital admissions, pregnancy and post-partum morbidity, sociodemographic characteristics of pregnant women, and number of capsules taken since the last visit. Each year, there were scheduled breaks of 4 weeks' duration over Christmas; eight rather than four capsules were distributed at the last visit before the break.

Field supervisors undertook verbal post mortems with close relatives or friends for deaths of trial participants and infants; these interviews included questions about the circumstances surrounding the death, an open history, and questions on signs and symptoms. Verbal

post mortems were reviewed by two experienced doctors, who independently coded the likely cause of death and (for women) whether it was pregnancy-related. If the doctors disagreed, the form was independently reviewed by a third doctor, and a consensus coding accepted if two of the three agreed. If there was no consensus on the cause of death, the three doctors met to see whether they could reach agreement. If, however, there was no consensus on a woman's pregnancy status, the form was reviewed by an experienced obstetrician, who assigned pregnancy status and cause of death.

Field supervisors were based at the four main district hospitals (in Kintampo, Nkoranza, Techiman, and Wenchi) from January, 2004, to capture data on hospital diagnosis, clinical signs, and management for any trial participants admitted while pregnant, delivering, or postpartum.

A random sample of 40 women was visited every week by specially trained IEC supervisors to gather data on sociodemographic characteristics, adherence to study capsules (including observation of capsules in their vial), exposure to IEC activities, and any perceived side-effects. The sample was selected to consist of ten women who should have had three capsules remaining in their vial, ten who should have had two, ten who should have had one, and ten who should have had none.

A substudy was undertaken during September and October, 2008, to assess vitamin A status of women in the trial, measured by serum retinol concentration. 440 pregnant women were selected at random from the trial database together with 440 women recorded as not pregnant for at least 12 months. Women were visited at home, and if they gave informed consent by signature or thumbprint, 5 mL of venous blood was taken by a trained phlebotomist. Serum retinol concentrations were measured by reverse-phase high-performance liquid chromatography at Kintampo Health Research Centre. Standard reference serum samples (SRM 968B, National Institute of Standards and Technology, Gaithersburg, MD, USA) were used to construct standard curves for determining retinol concentrations. Precision and accuracy between batches were checked by regular inclusion of samples from a designated control serum sample.

A survey was undertaken between March and May, 2003, to assess the extent of nightblindness in study participants. 200 women were selected at random for clinician review from 1466 women who reported problems with their vision during the monthly surveillance in February, 2003.

	Placebo group	Vitamin A supplementation group
Number of women recruited	103 297	104 484
Age (years)*		
<20	27 968 (27%)	28 779 (28%)
20–24	24 338 (24%)	24 541 (23%)
25–29	18 311 (18%)	18 475 (18%)
30–34	13 156 (13%)	12 975 (12%)
35–39	8840 (9%)	9098 (9%)
40–44	6669 (6%)	6551 (6%)
≥45	4015 (4%)	4065 (4%)
Number of women in random sample	4800	4640
Livebirths		
0	678 (14%)	658 (14%)
1	624 (13%)	616 (13%)
2	549 (11%)	560 (12%)
3	435 (9%)	465 (10%)
4	452 (9%)	385 (8%)
≥5	1139 (24%)	1079 (23%)
Not known	923 (19%)	877 (19%)
Highest educational level		
None	1274 (27%)	1284 (28%)
Primary school	739 (15%)	705 (15%)
Secondary school	1817 (38%)	1720 (37%)
Technical college or university	46 (1%)	51 (1%)
Not known	924 (19%)	880 (19%)
Marital status		
Married	2455 (51%)	2379 (51%)
Living together	418 (9%)	423 (9%)
Widow or divorced	345 (7%)	301 (6%)
Single, unmarried	646 (13%)	643 (14%)
Not known	936 (20%)	894 (19%)
Religion		
Christian	2901 (60%)	2820 (61%)
Muslim	693 (14%)	713 (15%)
Traditional African	103 (2%)	99 (2%)
Other	180 (4%)	131 (3%)
Not known	923 (19%)	877 (19%)
Ethnic group		
Akan	2075 (43%)	2042 (44%)
Other	1802 (38%)	1721 (37%)
Not known	923 (19%)	877 (19%)

Data are number or number (%). *On Jan 1, 2004.

Table 2: **Sociodemographic characteristics of study participants**

Outcomes

The primary outcomes of the trial were pregnancy-related mortality and all-cause female mortality. We used the International Classification of Diseases (ICD)-10 definition of pregnancy-related mortality (all deaths occurring during pregnancy, at delivery, or up to 42 days after delivery, irrespective of the cause or site).[25] Pregnancy-related mortality, expressed per 100 000 pregnancies, was chosen in preference to maternal mortality (which excludes coincidental deaths)[25] to enable comparison with the Nepal trial, and because pregnancy-related mortality does not require clinical diagnoses or post mortems to be undertaken. A pregnancy was eligible for inclusion provided both its outcome (livebirth, stillbirth, ectopic pregnancy, or pregnancy lost before 6 months) and the status of the

	Placebo group	Vitamin A supplementation group	Total
Home visits (every 4 weeks)			
Total number	4 215 234	4 265 396	8 480 630
Visits in which women were seen and capsules distributed (%)	3 587 164 (85·1%)	3 629 852 (85·1%)	7 217 016 (85·1%)
Adherence			
Visits in which capsule taking was checked (restricted to women seen both this month and previous month)	3 265 827	3 305 266	6 571 093
All four capsules taken last month (%)*			
Reported	88·2%	88·2%	88·2%
Based on capsules left in vial	84·1%	84·3%	84·2%
At least three capsules taken last month (%)*			
Reported	95·7%	95·8%	95·7%
Based on capsules left in vial	90·6%	90·9%	90·8%
Estimated adherence			
All four capsules taken last month (%)†			
Reported	75·1%	75·1%	75·1%
Based on capsules left in vial	71·6%	71·7%	71·7%
At least three capsules taken last month (%)†			
Reported	81·4%	81·5%	81·4%
Based on capsules left in vial	77·1%	77·4%	77·3%

*Percentage of visits with information on capsule taking. †Percentage of visits with capsules distributed multiplied by percentage of women taking capsules.

Table 3: **Adherence to study treatment**

	Placebo group	Vitamin A supplementation group	p value
Pregnant women			
Women sampled	217	223	..
Women tested*	130 (59·9%)	148 (66·4%)	..
Serum retinol (μmol/L)	1·18 (0·52)	1·12 (0·56)	0·15
<0·70 μmol/L	20 (15·4%)	37 (25·0%)	0·048
Non-pregnant women			
Women sampled	215	225	..
Women tested†	187 (87·0%)	197 (87·6%)	..
Serum retinol (μmol/L)	1·52 (0·77)	1·56 (0·77)	0·60
<0·70 μmol/L	18 (9·6%)	16 (8·1%)	0·60

Data are number, number (%), or mean (SD). *162 women were not tested: 123 pregnant women were not eligible because they had given birth between selection and testing; 13 refused consent; one had died; six had moved; seven were temporarily absent; and the reason was not recorded for 12 women. †56 women were not tested: seven were not eligible because they had become pregnant between selection and testing; 28 refused consent; one had died; two had moved; 14 were temporarily absent; and the reason was not recorded for four women.

Table 4: **Effect of weekly vitamin A supplementation on serum retinol concentration in pregnant and non-pregnant women**

woman 6 weeks after it ended were known. All-cause female mortality included all deaths in trial participants (including pregnancy-related deaths), expressed per 100 000 women-years of follow-up.

Secondary outcomes were severe maternal morbidity and perinatal and infant mortality. Serious maternal morbidity was defined as hospital admission during pregnancy or up to 42 days after delivery with the following diagnoses: severe pre-eclampsia, eclampsia, obstructed labour, emergency caesarean section, instrumental delivery, puerperal sepsis, spontaneous abortion, clinically significant malaria, clinically significant anaemia, antepartum haemorrhage, postpartum haemorrhage, or shock.

Perinatal and infant mortality consisted of stillbirth rate (babies born dead at 6 months of gestation or later) and perinatal mortality (number of stillbirths plus deaths in the first 7 days of life), both expressed per 1000 births (livebirths plus stillbirths); neonatal mortality (deaths in the first 28 days of life), expressed per 1000 livebirths; and infant mortality (deaths in the first year of life), expressed per 1000 infant-years of follow-up rather than per 1000 livebirths to take into account losses to follow-up during infancy. No changes were made to the study outcomes after commencement of the trial.

Trial monitoring

The conduct of the trial was overseen by the trial steering committee, which had 12 members chosen to facilitate uptake of any findings within Ghana and to provide technical support. The data monitoring and ethics committee had six members with expertise in cluster-randomised trials, epidemiology, medical statistics, obstetrics, community medicine, and maternal, newborn, and child health; they undertook yearly blinded safety analyses to check for any excess in primary or secondary mortality or severe morbidity outcomes in the vitamin A supplementation group, and a full interim analysis in June, 2006.

The data monitoring and ethics committee also monitored capsule content. 56 randomly selected batches of capsules (28 vitamin A and 28 placebo) covering all yearly consignments received from the manufacturers were tested at an independent laboratory in Cambridge, UK, and randomisation accuracy was confirmed. These samples included 14 batches of unused capsules (seven vitamin A and seven placebo) returned from the field that had been stored in uncontrolled conditions for at least 4 weeks. All vitamin A capsules tested, including those returned from the field, had at least 95% of the required retinol content (most had 100%), apart from three batches that were tested after substantial periods of storage; two batches of unused capsules tested more than 2 years after manufacture had 79% and 83% of their retinol content, and a batch tested after 4 years had 53%.

Statistical analysis

Sample size was determined by the rarest outcome, pregnancy-related mortality. Initial calculations suggested that data for 82 000 pregnancies would give 90% power to

detect a 33% reduction in pregnancy-related mortality in the vitamin A supplementation group (and 76 000 pregnancies an 80% power to detect a 30% reduction) from a baseline of 450 deaths per 100 000 pregnancies, at the 5% significance level. These calculations conservatively included a 10% design effect, which was expected to be negligible in view of the small cluster size and rare outcome. The data monitoring and ethics committee did conditional power calculations in 2003 and recommended that the trial be continued until October, 2008.

We undertook intention-to-treat analyses to compare treatment groups with random-effects regression to account for the cluster-randomised design. We used logistic models for outcomes where the denominator was pregnancies or births, and Poisson models where the denominator was person-years.

Intention to treat was defined by cluster of residence. When women moved residence, they received the same capsules as other women in their new residence, which might have resulted in them changing treatment group. We considered four periods to guide decisions for inclusion of data in the analysis. Lag referred to the period in which a woman was taking vitamin A supplements but the full effects of the intervention were not seen. During this period, events did not contribute to the analysis. Run-in was a shorter period at the start of the lag period during which vitamin A supplementation was likely to have little or no effect. Carry-over was defined as the period after cessation of vitamin A supplementation, when the effect was expected to be little reduced. During this period, women that changed from vitamin A supplementation to placebo could continue to contribute data to the vitamin A supplementation group. Wash-out, which was longer than the carry-over period, was the period after cessation of vitamin A supplementation, during which any effect would have worn off.

To ensure balanced lengths of follow-up between treatment groups, the same inclusion and exclusion rules needed to be applied whichever direction the change of group; equal values were therefore used for the lag and wash-out periods (6 months), and the run-in and carry-over periods (2 months). Since biochemical data do not exist to inform these values, they were decided in consultation with the data monitoring and ethics committee on the basis of responses from vitamin A experts.

Primary analyses therefore excluded the first 6 months after recruitment, and the 6 months after any change of treatment group, and regarded women as belonging to their pre-move group for a period of 2 months after changing group. Pure intention-to-treat analyses excluded data from the point that a woman changed group. Modified versions of both intention-to-treat and pure intention-to-treat analyses, undertaken for pregnancy-related mortality, included only women seen by their fieldworker (and given capsules) in at least three of the 6 months before the end of the pregnancy to increase the likelihood of detecting any true effect of vitamin A supplementation.

Mean serum retinol concentrations were compared by use of a *t* test and the proportions in each group with serum retinol concentrations of less than 0·70 μmol/L were compared with χ^2 tests. Analyses were done with Stata version 9.0.

	Placebo group	Vitamin A supplementation group
Intention-to-treat analysis*		
Number of pregnancies	39 234	39 601
Number of pregnancy-related deaths	148	138
Number of deaths per 100 000 pregnancies	377	348
Adjusted odds ratio† (95% CI)	1·00	0·92 (0·73–1·17)
p value	..	0·51
Modified intention-to-treat analysis‡		
Number of pregnancies	37 725	38 117
Number of pregnancy-related deaths	131	125
Number of deaths per 100 000 pregnancies	347	328
Adjusted odds ratio† (95% CI)	1·00	0·94 (0·74–1·21)
p value	..	0·65
Pure intention-to-treat analysis§		
Number of pregnancies	34 341	34 659
Number of pregnancy-related deaths	126	126
Number of deaths per 100 000 pregnancies	367	364
Adjusted odds ratio† (95% CI)	1·00	0·99 (0·77–1·28)
p value	..	0·95
Modified pure intention-to-treat analysis¶		
Number of pregnancies	33 031	33 379
Number of pregnancy-related deaths	110	115
Number of deaths per 100 000 pregnancies	333	345
Adjusted odds ratio† (95% CI)	1·00	1·04 (0·79–1·35)
p value	..	0·80

*Intention-to-treat analysis excludes first 6 months after recruitment or change of treatment group. †All odds ratios adjusted for clustering by use of random effects models. ‡Excluding women seen less than three times in the 6 months before end of pregnancy. §Excluding women after change of treatment group. ¶Excluding women after change of treatment group and excluding women seen less than three times in the 6 months before end of pregnancy.

Table 5: **Effect of weekly vitamin A supplementation on pregnancy-related deaths**

	Placebo group	Vitamin A supplementation group
Woman-years of follow-up*	289 310	292 560
All-cause adult female deaths	1298	1326
Mortality rate (per 100 000 years)	449	453
Adjusted rate ratio† (95% CI)	1·00	1·01 (0·93–1·09)
p value	..	0·85

Data are number unless otherwise indicated. *Woman contributed after 6 months in consistent treatment group, and continued to contribute to that group for a further 2 months if she moved. †Rate ratio adjusted for clustering by use of random effects models.

Table 6: **Effect of weekly vitamin A supplementation on all-cause female mortality (intention-to-treat analysis)**

	Placebo group	Vitamin A supplementation group
Pregnancies since Jan 1, 2004	30 380	30 055
Admissions in four main hospitals*	2342	2332
Adjusted odds ratio† (95% CI)	1·00	0·98 (0·89–1·09)
p value	..	0·74

Data are number unless otherwise indicated. *Admissions due to the following 12 causes: severe pre-eclampsia, eclampsia, obstructed labour, emergency caesarean section, instrumental delivery, sepsis after delivery, spontaneous abortion, clinically significant malaria, clinically significant anaemia, antepartum haemorrhage, postpartum haemorrhage, shock. †Odds ratios adjusted for clustering by use of random effects models.

***Table 7*: Effect of weekly vitamin A supplementation on pregnancy-related hospital admissions (intention-to-treat analysis)**

	Placebo group	Vitamin A supplementation group
Livebirths	36 710	37 042
Infant-years of follow-up	30 544	30 858
Stillbirths	1183	1241
Stillbirths (per 1000 births*)	31·2	32·4
Adjusted odds ratio† (95% CI)	1·00	1·04 (0·96–1·13)
p value	..	0·36
Perinatal deaths (stillbirths and deaths in first 7 days)	2083	2117
Perinatal mortality (per 1000 births*)	55·0	55·3
Adjusted odds ratio† (95% CI)	1·00	1·01 (0·94–1·08)
p value	..	0·85
Neonatal deaths (days 1–28)	1187	1140
Neonatal mortality (per 1000 livebirths)	32·2	30·8
Adjusted odds ratio† (95% CI)	1·00	0·95 (0·87–1·04)
p value	..	0·27
Infant deaths (0–11 months)	1963	1948
Infant mortality (per 1000 child-years)	64·3	63·1
Adjusted rate ratio† (95% CI)	1·00	0·98 (0·91–1·05)
p value	..	0·58

Data are number unless otherwise indicated. *Livebirths plus stillbirths. †All odds ratios and rate ratios adjusted for clustering by use of random effects models.

***Table 8*: Effect of maternal weekly vitamin A supplementation on rate of stillbirth and perinatal, neonatal, and infant mortality (intention-to-treat analysis)**

This trial is registered with ClinicalTrials.gov, number NCT00211341.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 1086 clusters in 272 fieldwork areas were randomised. 207 781 women were recruited, 101 191 (49%) at the start of the trial in their district, and the rest during the trial. In the last month of the trial (October, 2008), the mean cluster size was 108 women (SD 29·6; range 31–232). 1636 (1%) women withdrew consent and 89 196 (43%) moved out of the study area during the trial. Intention-to-treat analyses are based on 581 870 woman-years, 78 835 pregnancies, and 73 752 livebirths (figure 1). The number of participants recruited and followed up were similar between groups. Table 2 shows sociodemographic characteristics of study participants.

8 480 630 4-weekly home visits were made, with fieldworkers finding on average 85·1% of active women each cycle. Adherence to all four capsules was high (table 3) and similar for reports and vial observation (88·2% and 84·2%, respectively). Combination of the successful visit and adherence rates gives an overall estimated adherence of more than 70%. This level was stable throughout the trial and confirmed by random home visits; 7533 (80%) of 9440 women selected were successfully seen, 5936 (79%) of whom had taken their expected number of capsules.

Vitamin A supplementation did not seem to result in improved serum retinol concentrations in either pregnant or non-pregnant women (table 4), despite mean duration in the trial of 4·5 years (SD 2·3), and estimated mean compliance over 90% in the previous 12 months. Overall, 57 (21%) pregnant women and 34 (9%) non-pregnant women had moderate retinol deficiency (serum retinol concentration <0·70 µmol/L). 1466 (2%) of the 81 385 women seen in February, 2003, reported problems with their vision. None of the 124 women reviewed had clinical signs of xerophthalmia; four gave a history compatible with night blindness.

In the intention-to-treat analysis, there were 138 pregnancy-related deaths in the vitamin A supplementation group compared with 148 in the placebo group (adjusted odds ratio 0·92, 95% CI 0·73–1·17; table 5). Modified intention-to-treat, pure intention-to-treat, and modified-pure intention-to-treat analyses of pregnancy-related mortality are shown in table 5. The point estimates and lower confidence intervals increase as the analyses are restricted (with point estimates remaining close to 1·0). This pattern contrasts with what would be expected if vitamin A supplementation reduced pregnancy-related mortality, since both restrictions aim to remove potential sources of underestimation, by exclusion of data from women after they changed treatment groups and exclusion of women who had not been seen (and given capsules) regularly during pregnancy.

1326 women died of any cause in the vitamin A supplementation group compared with 1298 in the placebo group (adjusted rate ratio 1·01, 95% CI 0·93–1·09; table 6). There were no differences between groups in rates of pregnancy-related hospital admissions (table 7) or stillbirths, or in perinatal, neonatal, or infant mortality (table 8). All point estimates of adjusted rate ratios or odds ratios were close to 1·0, with narrow

95% CIs. Results are shown only for the primary intention-to-treat analyses; the restricted versions gave similar results. Adverse events were synonymous with the trial outcomes.

Discussion

Our results suggest that vitamin A supplementation once a week in women of reproductive age has no beneficial effect on their survival or on the survival of their babies in rural Ghana. The absence of an effect on stillbirth rate, neonatal survival, or infant survival accords with the findings of trials undertaken in Nepal[26] and Bangladesh.[18,27] However, the absence of an effect of vitamin A supplementation on pregnancy-related mortality contrasts with the substantial reduction in mortality reported in the Nepal trial, the only other trial in which all women of reproductive age were given supplements.

There are several possible reasons why our results differ from those of the Nepal trial. Night blindness (a sign of clinical vitamin A deficiency) was rare in participants in our trial, by contrast with the trial in Nepal, with approximately 10% of pregnant women in the placebo group affected.[28] There is also no word for night blindness in any of the local languages in Ghana, unlike in Nepal. This finding is unlikely to be the explanation for the difference between trial outcomes because subclinical levels of vitamin A deficiency were similar in the two trials (in our trial, 15% of pregnant women in the placebo group had moderate vitamin A deficiency compared with 19% in the Nepal trial).[15] Furthermore, there was no association between observed effect and vitamin A deficiency in trials of vitamin A supplementation in children;[14] reductions in mortality, hospital admissions, and severe diarrhoea were reported in children who received vitamin A supplements in Ghana,[7] where vitamin A deficiency was largely subclinical.

Vitamin A supplementation did not improve serum retinol concentrations in Ghanaian women. In fact, moderate vitamin A deficiency was more frequent in pregnant women in vitamin A supplementation clusters than in women in placebo clusters. The dose of retinol used in the vitamin A capsules was recommended as safe for pregnant women[22] and was slightly higher than the dose used in the Nepal trial. Analyses of capsules and high adherence rates suggest that women were receiving the intended dose; however, our results suggest that this dose was not sufficient to improve serum retinol concentrations in this setting. In Nepal, vitamin A supplementation substantially reduced moderate deficiency to 3% (compared with 19% in the placebo group), but supplementation with betacarotene did not (14% moderate vitamin A deficiency), although the reduction in mortality seen was higher in the betacarotene group than in the vitamin A group (figure 2).

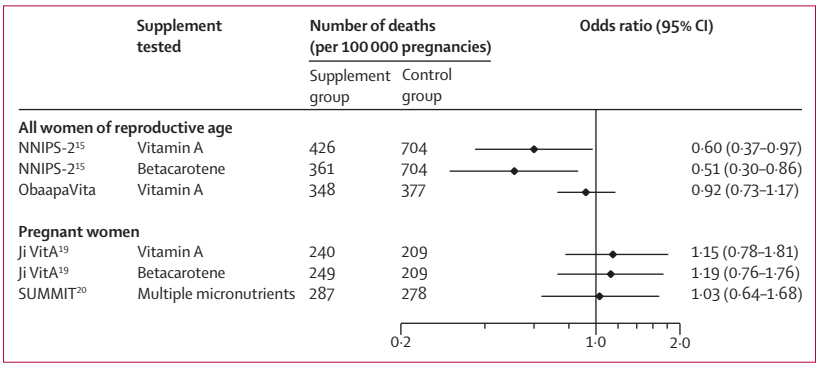

Figure 2: **Effect of vitamin A supplementation on maternal mortality in cluster-randomised trials**
NNIPS-2=Nepal Nutrition Intervention Project Sarlahi 2. SUMMIT=Supplementation with Multiple Micronutrients Intervention Trial.

Although capsule taking was not directly observed in our trial, as it was in Nepal, levels of adherence achieved by the IEC strategy seem to be similar. Both the random household visits to check adherence and formative research confirm that Ghanaian women were taking their capsules; in general, women attributed a range of positive benefits to the capsules irrespective of type (eg, being good for strength, protective against illness, and ensuring safe delivery[21]) and were concerned that they would no longer receive them after the trial. We estimated that on average 75% of women both received and took all four capsules every month; this proportion was higher (82%) for women in the serum retinol survey during the 12 months before blood samples were taken.

The high rates of migration recorded in our trial might have resulted in shorter participation times than those in the Nepal trial. However, women included in the main intention-to-treat analysis had been receiving the same type of capsules for a mean 31·8 months, with 80·6% of women receiving them for at least 12 months.

Migration within the trial area and the use of small geographical clusters resulted in a substantial proportion of women changing treatment groups during the course of the trial. This occurrence contrasts with the design of the trial in Nepal, in which arrangements were made to ensure women received the same type of supplements if they moved. Such an approach was not logistically feasible in Ghana because of the low population density and large area involved. Exclusion of data obtained after change of treatment group increased the adjusted odds ratio from 0·92 to 0·99, opposite to what would be expected if migration was causing an underestimation of the effect of vitamin A supplementation on mortality.

The reduction in pregnancy-related deaths seen in the trial in Nepal could be an anomalous finding even though the reduction was substantial and the p value small. This suggestion accords with the fact that the highest reductions were seen in deaths related to injury or of unknown or uncertain causes, with smaller

reductions recorded for deaths from obstetric causes or infection. We would be interested to know whether there were reductions or increases in the number of deaths unrelated to pregnancy in the Nepal trial, and whether there was a similar lack of any effect on all-cause adult female mortality, as seen in our trial.

Figure 2 summarises results of trials assessing the effects of vitamin A supplementation on pregnancy-related mortality. The Bangladesh trial tested the same supplements as did the Nepal trial, but only enrolled pregnant women; provisional results presented at the Micronutrient Forum in 2007 show non-significant increased mortality in women assigned to vitamin A or betacarotene supplementation compared with controls.[18] In the Supplementation with Multiple Micronutrients Intervention Trial in pregnant women in Indonesia, vitamin A supplementation had no effect on mortality compared with placebo.[19] The primary focus was, however, on fetal loss and early infant mortality, and the trial was not powered to detect an effect on maternal deaths; although the point estimate for the relative risk was close to 1, the confidence interval was wide.

Further trials to assess the effect of vitamin A supplementation on maternal mortality are unlikely to be undertaken because of their size and cost. The body of evidence, although limited, does not support inclusion of low-dose vitamin A supplementation for women in either safe motherhood or child survival strategies.

Contributors

The report was drafted by BRK and reviewed by all members of the ObaapaVitA Trial Team. It is dedicated to the late Paul Arthur who established Kintampo Health Research Centre and initiated the trial. PA, BRK, and OC designed the study. ZH and CT participated in design of the Information, Education, and Communication component of the trial. SAE, SD, BRK, and CH participated in design of the data management system. KE and LH designed the hospital data capture system. KE, LH, GtA, and SOA were responsible for trial conduct. CZ coordinated the fieldwork. CT managed the Information, Education, and Communication component. SAE, SD, CH, and JF managed the database. LH, CH, and JF undertook the statistical analyses.

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Conflicts of interest

We declare that we have no conflicts of interest.

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