Published in final edited form as:
Lancet. 2010 May 15; 375(9727): 1675–1677. doi:10.1016/S0140-6736(10)60443-6.

Vitamin A supplementation and maternal mortality

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In the 1980s, attention was drawn to the public health importance of vitamin A deficiency for child mortality.[1,2] Vitamin A supplementation is low cost, fairly easy to take to scale, and has saved many lives. In 1999, a trial in southern Nepal showed that supplementation with vitamin A or its precursor (betacarotene) in women of reproductive age reduced pregnancy-related mortality by 44%.[3] The findings were greeted sceptically:[4–6] there was no observable effect on infection-attributable mortality and the largest reduction seemed to be in deaths from burns, drowning, snakebite, and hanging; there were questions about logistics, safety, and potential cost-effectiveness; and there was disquiet about the use of pills rather than food to address malnutrition in women.

In *The Lancet* today, a large cluster-randomised, placebo-controlled trial in Ghana, from the ObaapaVitA Trial Team,[7] shows no benefit on maternal mortality of giving 25 000 IU of vitamin A as a weekly supplement to women of reproductive age. An astonishing 207 781 women were recruited to the trial, and the odds ratio for pregnancy-related mortality in the supplemented group was 0·92 (95% CI 0·73–1·17).

A recent large-scale replication trial in Bangladesh, which assessed supplementation for pregnant women rather than for all women of reproductive age, also reported no effect on pregnancy-related mortality,[8] as did a trial in Indonesia of multiple micronutrient supplementation with vitamin A.[9] As today's report concludes, the balance of evidence does not support inclusion of routine vitamin A supplementation for women in either safe motherhood or child survival strategies.

Several policy-relevant questions arise from the Ghana trial. Did the findings of the original Nepal trial arise by chance, might the substantial reduction in observed mortality be explained by higher baseline maternal mortality ratios than those in the Ghana and Bangladesh trials, or might they be explained by varying patterns of vitamin A deficiency between populations? If there are differential effects of mortality or deficiency, vitamin A supplementation, perhaps through dietary interventions rather than pills, might still be an effective option in high-mortality settings. It seems odd that vitamin A capsules in Ghana did not result in improved concentrations of serum retinol for either pregnant or non-pregnant women despite consumption for more than 4 years, compliance of over 90% in the previous 12 months, and the fact that 21% of pregnant women and 9% of non-pregnant women had moderate deficiency (serum retinol <0·70 μmol/L). Although serum retinol might not be a good index of vitamin A stores in non-deficient individuals,[10] 15% of pregnant women in the placebo group in Ghana were moderately deficient compared with 19% in Nepal. Night blindness (a sign of clinical vitamin A deficiency) was not recorded in the Ghana trial but was common in Nepal, with about 10% of pregnant women in the placebo group affected. This difference might be crucial if more maternal deaths occur in the subgroup of women with night blindness. The Ghana trial reports no effect of

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We declare that we have no conflicts of interest.

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supplementation on hospital admissions for 12 maternal complications, but it would be interesting to know if there was any specific effect on sepsis after delivery.

Second, does the Ghana trial finally rule out an effect of vitamin A supplementation in pregnancy on newborn or early infant mortality? Yes. The trial found no measurable effects on stillbirths, newborn deaths, or perinatal mortality, and nor did the Nepal or Bangladesh trials.[3,8] The issue of whether newborn supplementation reduces early infant mortality in deficient populations is more questionable. A systematic review included six trials from low-income countries and showed no overall benefit despite two positive Asian trials;[11] recent work from Guinea-Bissau supports this finding and raises the possibility of a negative effect on the survival of female infants.[12,13] There is also concern that large-scale implementation might compromise the potential benefits shown in smaller scale trials.[14]

Third, has the time come to evaluate ways to increase food intake in pregnancy, rather than intake of individual or multiple micronutrients? The green revolution in India ended last century. Since 2000, per hectare yield of wheat, rice, and cereals has declined after an upward trend for 50 years.[15] Pulse consumption has fallen from 27 kg per head in the 1960s to 11 kg per head now. As the economist Utsa Patnaik observes, “the average Indian family of five in 2005 was consuming a staggering 110 kg less grain per year compared with 1991, reflecting divergent trends: a sharp rise in intake for the wealthy minority, outweighed by a large decline for the majority. Not only has calorie intake per capita fallen, there is also a steep decline in protein intake for four-fifths of the rural population over the period 1993–94 to 2004–05”.[16]

Finally, evaluation of new interventions to reduce maternal mortality is a high priority in view of the lack of progress towards Millennium Development Goal 5. The ObaapaVitA Trial Team are to be congratulated for their commitment to its measurement as a primary outcome. We need more of these trials across a range of interventions, but they have to be large. Maternal deaths, even in high-mortality settings, are fairly rare events and trial groups might need to include 100 000 pregnancies or more. If we are to provide policy makers with new options, how can we design trials that can be completed within a reasonable timeframe? It took 10 years to confirm that vitamin A supplementation in childhood improved survival, and it has taken more than 15 years to resolve the question of its effects on maternal mortality. To get results within 3 years will require multisite trials, simple surveillance procedures to measure maternal deaths in communities, and donors willing to put up millions of pounds for studies that cover large and poor populations. There have been few trials of interventions to reduce maternal mortality ratios, and we need new evidence of effectiveness at scale if we are to reduce the unacceptable toll of maternal mortality.

Acknowledgments

We acknowledge our friendship and admiration for the late Paul Arthur, who led the establishment of the ObaapaVitA Trial.

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