

Letters to the Editor

Response to the commentary: Postpartum vitamin A supplementation and infant mortality

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In response to the commentary¹ on our systematic review,² we would like to clarify the following aspects. The intent of our systematic review² was to strengthen the evidence base for articulation of appropriate global policy on maternal postpartum vitamin A supplementation (VAS) in developing countries. We therefore evaluated the effect of VAS in postpartum mothers (in any dose), irrespective of antenatal VAS status, on mortality, morbidity and adverse effects in their infants until the age of 1 year. The review was not designed to only specifically determine the effects of maternal VAS in doses recommended by either the WHO³ or a later technical consultation.⁴ The objectives and methodology of our review had been approved after a stringent peer review process.⁵

We disagree that the ‘meta-analysis was based on diverse data of limited utility for discerning a mortality impact’. Variation among participants, settings and interventions occurs in most, if not all, systematic reviews. In spite of such clinical diversity, there was no statistical heterogeneity ($I^2=0\%$, $P=0.9$) across trials indicating the consistency in findings for infant mortality. On including a subsequent large trial⁶ also, there was no evidence of reduced infant mortality [random effect risk ratio (RR) 1.0, 95% confidence interval (CI) 0.94–1.06, $P=0.9$] or heterogeneity ($I^2=0\%$, $P=0.9$). This evidence from 96203 participants in seven trials was of high quality (further research is very unlikely to change our confidence in the estimate of effect) as per GRADE guidelines⁷ recommended by Cochrane collaboration.

The review’s methodology and conclusions cannot be discredited on the following two critiques. The report of one trial perceived to be of ‘appropriate sample size’ in ‘an HIV infected population’ pertains to only HIV-negative mothers.⁸ Even in trials providing small weekly doses of vitamin A, the cumulative dose was 200 000 IU, equivalent to the mega-dose recommended by the WHO.³ The later technical consultation⁴ states: ‘as an alternative to large-dose supplementation, mothers can receive vitamin A at any time postpartum, given as a low dose not exceeding 10 000 IU per day or 25 000 IU per week’.

We reiterate that following maternal postpartum VAS, there is no evidence of mortality (high-quality evidence) or morbidity benefits to the infant; these considerations would not alone be sufficient justification for initiating this intervention in public health programmes. However, policy formulation would be based on deliberation of additional consequences including improvement of maternal and infant vitamin A status, maternal benefits (morbidity or mortality), safety and cost-effectiveness.

Further, we clarify the following inconsistencies in referring to our ‘parallel meta-analysis effort’ on neonatal VAS.⁹ The intervention in participants was restricted to the neonatal period (<1 month age as per standard international nomenclature) and did not extend into ‘early infancy’ as implied in the commentary. In a *post hoc* analysis mentioned in the Discussion section,⁹ we had found no convincing evidence of reduced mortality during infancy for dosing during the first 48 h after birth (random effect RR 0.89, 95% CI 0.73–1.09, $P=0.256$; $I^2=56\%$).

It is inappropriate and premature to contemplate regional newborn VAS or its dovetailing with maternal postpartum VAS. The tendency to influence global policy on the basis of successive subgroup analyses (first 48 h of the neonatal period in participants restricted to a region) needs strong and immediate discouragement. Global policy formulation must await further input from all the four ongoing trials.^{10–13}

References

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Comment on: 'Maternal postpartum vitamin A supplementation for the prevention of mortality and morbidity in infancy: a systematic review of randomised controlled trials'

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I read the meta-analysis by Gogia and Sachdev¹ with great interest, and I believe it is a very important demonstration of the gap between research and policy. Although maternal vitamin A supplementation in the postpartum period has been recommended since many years, there is limited scientific evidence for its benefits.

As concluded by Gogia and Sachdev, the rationale for the policy is not found in the effect on infant mortality and morbidity. The authors add that a rationale may 'be based on deliberation of additional consequences, including improvement of maternal and infant vitamin A status, maternal benefits (morbidity or mortality), maternal safety and cost-effectiveness' but also write that 'Only prevention of infant morbidity or mortality would be sufficient justification for initiating this intervention in public health programs'. Like the authors, I believe policy should be based on mortality and morbidity outcomes and not on improved vitamin A status.

It would be interesting to know, however, if the effect of maternal supplementation on infant mortality was the same in male and female offspring since neonatal supplementation has shown sex-differential effects, with a possible beneficial effect in boys but a negative one in girls.^{2–5} Overall 'no effect' may hide

underlying sex-differential effects going in opposite directions.

It should also be kept in mind that the real-life effects of a maternal vitamin A supplementation policy may not yield the same effect as found in controlled studies. Compliance may be lower and errors occur, as the following example illustrates:

Guinea-Bissau recently implemented the maternal vitamin A supplementation policy. At a health centre in the capital Bissau, the task was transferred from midwives to nurses working with the Expanded Program of Immunisations as the nurses would see the mothers postpartum when the mothers brought their children for the first vaccinations.

However, something went wrong, and instead of supplementing the mothers, the nurses gave the supplements to children who were <6 weeks of age when they came for vaccinations.

Hence, the supplement of 200 000 IU vitamin A that was intended for the mothers ended up being given to the infants instead. Based on the meta-analysis by Gogia and Sachdev and what is known about supplementing African neonates with high-dose vitamin A supplements,^{2,3,6,7} the intended treatment holds no benefit for the children and the real-life implementation could be dangerous.