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# Postnatal Vitamin A Supplementation in Developing Countries: An Intervention Whose Time Has Come?

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**I**N THIS MONTH'S *Pediatrics* Electronic Pages, Klemm et al<sup>1</sup> have provided new information that demonstrates a mortality benefit to neonatal vitamin A supplementation (VAS) in a developing country. Although nearly 100 years have passed since vitamin A was discovered, and more than 60 years since it was first synthesized, the precise mechanisms of its beneficial effects as a supplement remain to be elucidated. Beginning with trials reported in the 1980s,<sup>2</sup> VAS in children  $\geq 6$  months of age has been accepted as a cost-effective intervention that is associated with a significant decrease in all-cause mortality in children aged 6 to 59 months in areas of highly prevalent vitamin A deficiency.<sup>3</sup> It is estimated that in 1999 VAS prevented 242 000 childhood deaths worldwide at an incremental cost of \$64 per death averted and \$0.02 per dose.<sup>4</sup> Few significant adverse effects have been reported. VAS has been shown to be effective in reducing chronic lung disease in very low birth weight infants.<sup>5</sup> However, not all studies have been positive; trials have shown no benefit of VAS in infants aged 1 to 5 months.<sup>6</sup>

The evidence for postnatal VAS in neonates born near term has been mixed. Klemm et al administered 50 000 IU of vitamin A to infants within the first month of life in Bangladesh, a large majority of whom were born at home.<sup>1</sup> The relative risk of all-cause mortality (0.70–1.00) was reduced by 15% ( $P = .045$ ) for those who received VAS versus placebo, and the trial was stopped early after the survival benefit became apparent. This positive outcome is consistent with 2 earlier trials, 1 in Indonesia<sup>7</sup> and another in south India,<sup>8</sup> in which newborns dosed similarly also experienced reductions in mortality during the first months of life. On the other hand, these encouraging findings have not been duplicated in Africa. Perinatal VAS in a recent trial in Guinea-Bissau failed to achieve a benefit in mortality.<sup>9</sup> An earlier randomized trial in Zimbabwe also showed no survival advantage for infants given VAS at birth.<sup>10</sup>

Various factors are involved that could confound the evidence supporting the benefit of VAS in neonates. For example, there is controversy about the effects that VAS has on the response to vaccines when given concomitantly with immunizations between the ages of 1 and 5 months. Insufficient data are currently available to demonstrate the effects of single-dose neonatal VAS on response to subsequent vaccinations.<sup>11</sup> The prevalence of vitamin A deficiency in mothers and their infants varies greatly between regions, which has yielded differential responses to neonatal supplementation programs. A high prevalence of diseases including HIV, measles, and

other infections may affect the efficacy of neonatal programs. Humphrey et al reported that VAS given at birth to either mothers or their HIV-exposed infants in Zimbabwe who were polymerase chain reaction–negative at 6 weeks doubled mortality by 2 years of age.<sup>12</sup> However, there was a mortality benefit in infants given VAS at birth who were HIV-positive at baseline. Genetic factors that may affect response to VAS have been identified in both human<sup>13</sup> and animal<sup>14</sup> studies. Benn et al<sup>15</sup> have pointed out that boys seem to derive greater benefit from VAS than girls. This may be a result of greater vitamin A deficiency in boys, gender-related immunologic differences, or differential response to vaccines administered with VAS. It is worth noting that in the study by Klemm et al an opposing trend was reported: female infants seemed to benefit more than the male infants.<sup>1</sup>

Klemm et al conducted a large, rigorous study in Bangladesh under difficult conditions. Given the lack of efficacy of VAS seen in infants aged 1 to 5 months in earlier studies, it seems that giving the supplementation close to birth is important. An open question is whether the level of public health coordination required to provide VAS within the first 24 hours of life is achievable in resource-poor countries, where most births occur at home. An encouraging sign in Bangladesh is the fact that since the 1980s the rate of BCG vaccination, targeted to be given at birth, rose from 2% to 95% by 2000,<sup>16</sup> which raises hope that VAS and BCG vaccine could be administered concurrently after delivery.

In the Klemm et al study, an interesting observation was that there was a positive benefit even for those infants who were dosed nearly 1 month after birth. This finding needs to be understood in light of earlier studies that showed no benefit in VAS administered with vaccinations from the ages of 1 to 5 months. The effects of single versus multiple dosing, immunization interactions, susceptibility to infection, and age-dependent response to VAS all could be involved in explaining these different results. Although there was a benefit seen in infants who were receiving VAS even if their mothers

**Abbreviation:** VAS, vitamin A supplementation

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were enrolled in the placebo arm of a concomitant weekly, low-dose VAS trial during pregnancy, it would be instructive to know if additional maternal factors, such as the effects of peripartum maternal retinol, affected infant survival.

It is clear that we have much to understand about neonatal VAS. In southern Asia, which has a relatively low overall rate of HIV infection compared with sub-Saharan Africa, there is a mortality benefit. It seems appropriate to move ahead with implementation of neonatal VAS as a public health policy in regions where it has been shown to have a survival benefit. However, implementation of programs should not proceed in any specific geographic area until controlled trials have shown a benefit in that region. Research that elucidates the underlying mechanisms of VAS and individual factors that may modify its benefit, such as gender, interaction with immunizations, coinfections, or exposure to diseases such as HIV and genetic and maternal factors, needs to continue. The goal should be to understand the effects and mechanisms of VAS adequately so that infants can be chosen for or excluded from supplementation on the basis of a defined set of criteria.

Neonatal VAS seems to be an intervention that holds promise in accomplishing a step-wise reduction in infant mortality in some resource-poor regions of the world, where successes have been difficult to achieve. However, we agree with others that caution and additional trials are needed before global use of such a program is undertaken.<sup>17</sup>

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