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Maternal vitamin A: Effects on mothers, effects on offspring

Vitamin A deficiency can compromise maternal health and survival and offset child development in poor societies.

In Gangetic South Asia, vitamin A deficiency contributes to maternal undernutrition during pregnancy and lactation¹. However, while known to exist, the need to estimate its extent, severity and health consequences, and the public health benefits of prevention, among mothers and children is an urgent research priority. Over the past two decades the Center for Human Nutrition of the Johns Hopkins Bloomberg School of Public Health (JHU) has been investigating this nutritional problem in rural South Asia, with support of the Bill and Melinda Gates Foundation and USAID, by conducting community intervention trials and epidemiological studies in its two large population research sites, in Nepal (Nepal Nutrition Intervention Project - Sarlahi, or NNIPS) and Bangladesh (The JiVitA Project)². The goals of the research have been to inform and guide policies and programs for preventing vitamin A deficiency and its short and long term consequences among mothers and their offspring throughout the region.

Maternal night blindness

Along the southern rural plains of Nepal, in the district of Sarlahi, home to a quarter of a million people, JHU's studies have revealed that 10-15% of pregnant women develop night blindness, a visual disturbance during twilight attributable to vitamin A deficiency^{3,4}. Women with night blindness are far more likely to have health problems than those with normal night time vision, reflected by a greater chance of being biochemically vitamin A-deficient, wasted, anemic and ill with infections during pregnancy⁴. Night blind mothers face a higher risk of their infants dying in the first half of infancy than

non-night blind gravida⁵ and a far higher risk of their own mortality, largely due to infection, for up to two years following pregnancy in comparison to pregnant women without the condition (*Figure*)⁶. This extended health risk exists even though the inability to see at night often resolves shortly after giving birth. That is, the health risk associated with this condition persists long after the clinical symptom disappears.

Given that night blindness can be gleaned from a simple, standardized history, these findings in Nepal, which have been corroborated by studies in India^{7,8} and elsewhere, led the International Vitamin A Consultative Group to issue policy briefs during the past decade warning of its existence in pregnancy and offering methods and cutoffs for its assessment⁹. The findings led the Demographic Health Surveys over the past decade to include a history of maternal night blindness in its core module that has generated country prevalence rates and formed the basis for the most recent World Health Organization estimates of there being nearly 10 million pregnant women at a given time with night blindness, among an estimated 19 million with physiologically significant vitamin A deficiency in low income countries¹⁰.

Effects of maternal vitamin A supplementation

Nepal: A major question of the past 15 years has been whether maternal vitamin A supplementation could reduce health risks and improve maternal and infant survival?

A first trial carried out by JHU among ~22,000 pregnancies in Sarlahi District, Nepal, showed that weekly, maternal supplementation with vitamin A, either "preformed" or in the form of its plant precursor beta-carotene, given to meet recommended dietary levels before, during and following pregnancy, could reduced maternal mortality by ~44%, from 704 to 385 deaths per 100,000 pregnancies¹¹ (Table). No overall impact was observed on infant mortality, except among babies born to mothers prone to night blindness, whose risk of death was markedly reduced by maternal vitamin A supplementation¹². Longer term effects, however were apparent among offspring. Specifically, a ~10 year follow-up study supported by the Gates Foundation was the first to observe an increase in lung capacity among preadolescent children whose mothers received weekly vitamin A supplements versus placebo¹³, a finding predicted from decades of animal studies. Further, children born to vitamin A supplemented mothers exhibited a higher circulating level of natural antibodies, derived from cell lines that tend to mature in number in early infancy¹⁴, a finding also supported by experimental findings in animals. It is equally plausible that hearing loss could have been lowered, stemming from the vitamin's role in regulating middle and inner ear development, but this has not yet been examined. Other health and development outcomes that have been assessed, including blood pressure, metabolic syndrome¹⁵ and cognition, have not been found to be affected at prepubescent ages.

Bangladesh: The mortality impact observed in Nepal spurred wider interest to extend the findings to other undernourished settings. At the turn of the millennium, JHU set up the JiVitA site in northern Bangladesh² [see Brief No. 1] where a second, placebo-controlled

trial (JiVitA-1) of weekly vitamin A or beta-carotene supplementation was conducted among 60,000 enrolled mothers. Neither a reduction in maternal or infant mortality was observed¹⁶. The lack of maternal mortality impact has been attributed to contextual differences¹⁷. In Bangladesh, the mortality rate of women related to pregnancy turned out to be far lower, ~30% that seen in Nepal (231 per 100,000) (Table), which was accompanied by a more varied and nutritious diet, a lower prevalence of vitamin A deficiency (~7% vs 19%) and a higher birth attendance rate. However, other health benefits are emerging, such as a recently reported 30-40% lower incidence of bacterial vaginosis among vitamin A or beta-carotene versus placebo supplemented mothers¹⁸, a finding that is consistent with a known role for vitamin A in maintaining the integrity of the epithelial linings of the cervix and vagina¹⁹. Bacterial vaginosis has been estimated to affect ~8% of all pregnant women and is a risk factor for preterm birth¹⁸. Analyses are underway to explore additional plausible effects of maternal supplementation. [A third trial, in Ghana, has also not observed a significant reduction in maternal mortality with weekly vitamin A supplementation, likely reflecting population differences in risks of vitamin A deficiency, maternal mortality and other risk factors¹⁷].

Findings from JiVitA-1 and the earlier NNIPS-2 trials continue to reveal new evidence on how maternal and early life micronutrient exposures, including vitamin A, can influence short and long term health and survival in the vast, population dense Gangetic flood plains of South Asia.

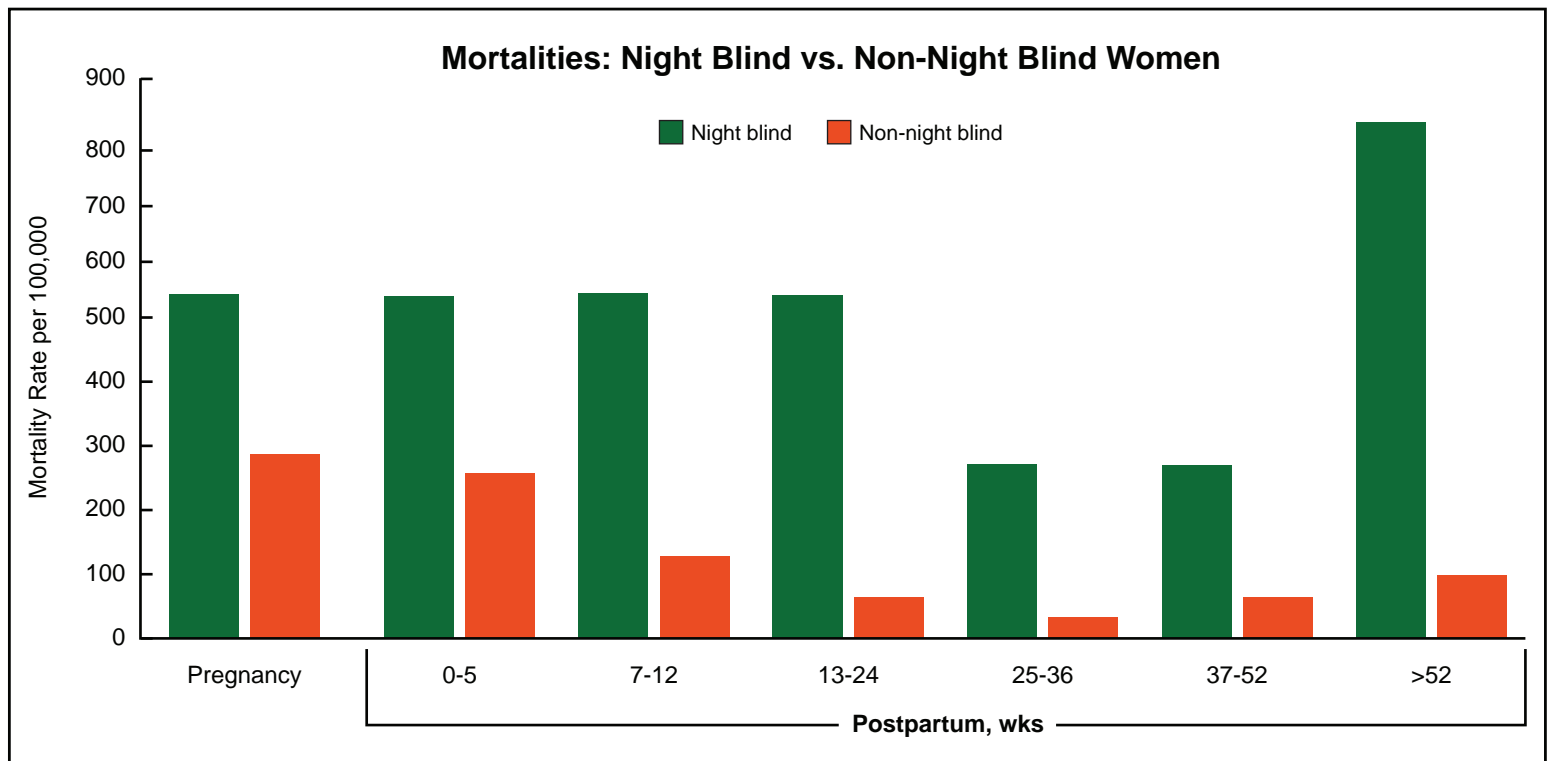


Figure. Period-specific mortality rate per 100,000 pregnancies among night blind and non-night blind women in placebo group in the NNIPS-2 randomized maternal vitamin A or beta-carotene supplementation trial in Sarlahi, Nepal, 1994-97⁵.

	Placebo	Vitamin A	β -carotene
Nepal (NNIPS-2)⁸			
No. of Pregnancies	7,241	7,747	7,201
No. of Deaths	51	33	26
Mortality rate [†]	704	426	361
RR	1.00	0.60	0.51
95% CI	–	(0.37-0.97)	(0.30-0.86)
P-value		<0.04	<0.01
Bangladesh (JiVitA-1)¹			
No. of Pregnancies	19,862	19,806	19,998
No. of Deaths	41	47	50
Mortality rate [†]	206	237	250
RR	1.00	1.15	1.21
95% CI	–	(0.75-1.76)	(0.81-1.81)
P-value		0.52	0.35
[†] per 100,000 live births			

References

- West KP Jr. Extent of vitamin A deficiency among preschool children and women of reproductive age. *J Nutr* 2002;132:2857S-2866S.
- Labrique AB, Christian P, Klemm RD, Rashid M, Shamim AA, Massie A, Schulze K, Hackman A, West KP Jr. A cluster-randomized, placebo-controlled, maternal vitamin A or beta-carotene supplementation trial in Bangladesh: design and methods. *Trials* 2011;12:102-118.
- Katz J, Khattry SK, West KP, Humphrey JH, Leclercq SC, Kimbrough E, Pokhrel PR, Sommer A. Night blindness is prevalent during pregnancy and lactation in rural Nepal. *J Nutr* 1995;125:2122-2127.
- Christian P, Khattry SK, Katz J, Shrestha SR, Pradhan EK, LeClerq SC, West KP Jr. Night blindness of pregnancy in rural Nepal - nutritional and health risks. *Intl J Epidemiol* 1998;27:231-237.
- Christian P, West KP Jr, Khattry SK, LeClerq SC, Kimbrough-Pradhan E, Katz J, Shrestha SR. Maternal night blindness increases risk of infant mortality in the first 6 months of life among infants in Nepal. *J Nutr* 2001;131:1510-1512.
- Christian P, West KP Jr, Khattry SK, Kimbrough-Pradhan E, LeClerq SC, Katz J, Shrestha SR, Dali SM, Sommer A. Night blindness during pregnancy and subsequent mortality among women in Nepal: Effects of vitamin A and β -carotene supplementation. *Am J Epidemiol* 2000;152:542-547.
- Katz J, Tielsch JM, Thulasiraj RD, Coles C, Sheeladevi S, Yanik EL, Rahmathullah L. Risk factors for maternal night blindness in rural South India. *Ophthalmic Epidemiol* 2009;16:193-197.
- Tielsch JM, Rahmathullah L, Katz J, Thulasiraj RD, Coles C, Sheeladevi S, Prakash K. Maternal night blindness during pregnancy is associated with low birthweight, morbidity, and poor growth in South India. *J Nutr* 2008;138:787-792.
- Christian P. Maternal night blindness: a new indicator of vitamin A deficiency. IVACG Statement. ILSI Research Foundation, Washington DC, April 2002.
- WHO. Global prevalence of vitamin A deficiency in populations at risk 1995-2005. Geneva:WHO, 2009.
- West KP Jr, Katz J, Khattry SK, LeClerq SC, Pradhan EK, Shrestha SR, Connor PB, Dali SM, Christian P, Pokhrel RP, Sommer A. Double blind, cluster randomised trial of low dose supplementation with vitamin A or β -carotene on mortality related to pregnancy in Nepal. *BMJ* 1999;318:570-575.
- Christian P, West KP Jr, Khattry SK, Katz J, LeClerq SC, Kimbrough-Pradhan EK, Katz J, Shrestha SR. Maternal night blindness increases risk of mortality in the first six months of life among infants in Nepal. *J Nutr* 2001;131:1510-12.
- Checkley W, West KP Jr, Wise RA, Baldwin MR, Wu L, LeClerq SC, Christian P, Katz J, Tielsch JM, Khattry S, Sommer A. Maternal vitamin A supplementation and lung function in offspring. *NEJM* 2010;362:1784-1794.
- Palmer AC. Nutritionally mediated programming of the developing immune system. *Adv Nutr* 2011;2:377-95.
- Stewart CP, Christian P, Katz K, Schulze KJ, Wu LSF, LeClerq SC, Shakya TR, Khattry SK, West KP Jr. Maternal supplementation with vitamin A or beta-carotene and cardiovascular risk factors in pre-adolescent children in rural Nepal. *J DOHaD* 2010;doi:10.1017/S2040174410000255.
- West KP Jr, Christian P, Labrique AB, Rashid M, Shamim AA, Klemm RD, Massie AB, Mehra S, Schulze KJ, Ali H, Ullah B, Wu LS, Katz J, Banu H, Akhter HH, Sommer A. Effects of vitamin A or beta-carotene supplementation on pregnancy-related mortality and infant mortality in rural Bangladesh: A cluster-randomized trial. *JAMA* 2011;305:1986-1995.
- West KP Jr. Reflections on differences in impact of vitamin A on maternal mortality: the role of context. *Sight and Life* 2011;25 (3):64-69.
- Christian P, Labrique AB, Ali H, Richman MJ, Wu L, Rashid M, West KP Jr. Maternal vitamin A and beta-carotene supplementation and risk of bacterial vaginosis: a randomized controlled trial in rural Bangladesh. *Am J Clin Nutr* 2011;94:1643-9.
- Darwiche N, Celli G, De Luca LM. Specificity of retinoid receptor gene expression in mouse cervical epithelia. *Endocrinology* 1994;134:2018-25.
- Kirkwood BR, Hurt L, Amenga-Etego S et al. Effect of vitamin A supplementation of women of reproductive age on maternal survival in Ghana (ObaapaVitA): cluster-randomised, placebo-controlled trial. *Lancet* 2010;375:1640-9.

JiVitA is a project of the Center for Human Nutrition of Johns Hopkins University, spanning 19 unions of Gaibandha and Rangpur Districts in rural Northwestern Bangladesh. JiVitA has been conducting community trials, supported by epidemiologic, ethnographic, and laboratory research since 2000, to reveal the impact of public health interventions in order to guide nutrition and health programs and policies in Bangladesh and elsewhere in South Asia.



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For Further Information Contact

Center for Human Nutrition
Department of International Health
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD 21205

Telephone: 1-410-955-2061

<http://www.jhsph.edu/chn>



The JiVitA Project
Johns Hopkins University
Road 25, Block A, House 48, Flat C-1
Banani, Dhaka, Bangladesh

NEW Telephone: (+88-02) 9840091

<https://www.jivita.org>