Vitamin A Deficiency, Iron Deficiency, and Anemia Among Preschool Children in the Republic of the Marshall Islands

Neal A. Palafox, MD, MPH, Mary V. Gamble, PhD, Barbara Dancheck, BS, Michelle O. Ricks, MS, Kennar Briand, MBBS, and Richard D. Semba, MD, MPH

From the Department of Family Practice and Community Health, John A Burns School of Medicine, University of Hawaii, Honolulu, Hawaii, USA; the Department of Environmental Health Sciences, Columbia University School of Public Health, New York, New York, USA; the Ministry of Health and Environment, Republic of the Marshall Islands; and the Department of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

OBJECTIVE: We investigated the co-occurrence of vitamin A deficiency, iron deficiency, and anemia among young children in the Republic of the Marshall Islands.

METHODS: Hemoglobin, serum retinol, and serum ferritin were assessed in the Republic of the Marshall Islands Vitamin A Deficiency Study, a community-based survey that involved 919 children ages 1 to 5 y.

RESULTS: The proportion of children with vitamin A deficiency (serum retinol concentrations < 0.70 μM/L) was 59.9%. The prevalences of anemia (hemoglobin < 110 g/L), iron deficiency (serum ferritin < 12 μg/L), and iron deficiency anemia (iron deficiency and anemia) were 36.4%, 53.5%, and 23.8%, respectively. The proportion of children who had co-occurrence of vitamin A and iron deficiencies was 33.2%. The mean ages of children with and without vitamin A deficiency were 3.2 ± 1.4 and 2.9 ± 1.5 y, respectively ($P = 0.01$), and the mean ages of those with and without iron deficiency were 2.7 ± 1.3 and 3.5 ± 1.4 y, respectively ($P < 0.0001$).

CONCLUSIONS: Children in the Republic of the Marshall Islands, ages 1 to 5 y, are at high risk of anemia, vitamin A deficiency, and iron deficiency, and one-third of these children had the co-occurrence of vitamin A and iron deficiencies. Further investigation is needed to identify risk factors and evaluate interventions to address vitamin A and iron deficiencies among children. *Nutrition* 2003;19:405–408. ©Elsevier Inc. 2003

KEY WORDS: anemia, children, ferritin, iron deficiency, Marshall Islands, retinol, vitamin A deficiency

INTRODUCTION

In many developing countries worldwide, young children are at a high risk of vitamin A deficiency and iron deficiency. Vitamin A deficiency affects an estimated 253 million preschool children worldwide.[1] The consequences of vitamin A deficiency include growth failure, depressed immunity, higher risk of xerophthalmia and blindness, anemia, and increased morbidity and mortality from some infectious diseases.[2,3] Iron deficiency is a major problem among preschool children worldwide, and consequences of iron deficiency include retarded psychomotor development, impaired cognitive function, and anemia.[4,5]

In the past 12 y, epidemiologic surveys have shown that some islands in the South and Western Pacific regions have the highest prevalence rates of clinical vitamin A deficiency that have been recently described.[6] In reports from some islands, the rates of clinical vitamin A deficiency, i.e., nightblindness and Bitot spots, exceeded 15%.[6] Rapid demographic change, poverty, lack of homestead food production, and replacement of traditional foods such as breadfruit, banana, taro, yam, sweet potato, coconut, and fish with rice and sweet refined foods of low nutritional quality have been implicated in the recent epidemic of nutritional blindness.[6] In the Republic of the Marshall Islands, a nation consisting of 29 atolls including 1225 islands, a national nutrition survey in 1991 showed that the prevalence of anemia was high among children.[7]

Although vitamin A deficiency and iron deficiency are two major micronutrient deficiencies occurring among preschool children in developing countries, few recent epidemiologic studies have addressed the prevalence of these two deficiencies simultaneously in the same population.[8] We hypothesized that iron deficiency and vitamin A deficiency were highly prevalent among young children in the Republic of the Marshall Islands and that the co-occurrence of both deficiencies among children was common. To address these hypotheses, we conducted a community-based survey of vitamin A deficiency, iron deficiency, and anemia among children ages 1 to 5 y in the Republic of the Marshall Islands.

MATERIALS AND METHODS

A community-based survey, the Republic of the Marshall Islands Vitamin A Deficiency Study, was conducted between November 1994 and March 1995. The total survey included 919 Marshallese children, ages 1 to 5 y, from 10 atolls, who represented approxi-

This study was supported by The Pacific Health Research Institute; UNICEF; Fergussen Foundation Hawaii; Hawaii Community Foundation, Ministry of Health and Environment, Republic of the Marshall Islands; the National Institute of Child Health and Human Development (HD30042); the National Institutes of Health; and the United States Agency for International Development (Cooperative Agreement HRN A-0097-00015-00).

Correspondence to: Richard D. Semba, MD, MPH, 550 North Broadway, Suite 700, Baltimore, MD 21205, USA. E-mail: rdsemba@jhmi.edu

0899-9007/03/$30.00
doi:10.1016/S0899-9007(02)01104-8

TABLE I.

PREVALENCE OF VITAMIN A DEFICIENCY, IRON DEFICIENCY, AND ANEMIA IN THE STUDY POPULATION BY ATOLL

Atoll	*n*	Age (y), mean (SD)	Female (%)	Anemia (%)*	Vitamin A deficiency (%)†	Iron deficiency (%)‡	Iron deficiency, anemia (%)§	Vitamin A + iron deficiencies
Ailuk	38	2.89 (1.55)	50.0	36.8	47.3	50.0	36.3	27.3
Arno	87	3.13 (1.37)	40.2	47.7	67.8	46.7	25.8	29.0
Enejelar	11	2.63 (1.62)	63.6	9.1	45.4	54.5	9.1	18.2
Enewetak	67	3.17 (1.35)	53.7	26.9	56.7	42.4	16.6	22.7
Kwajalein	259	3.24 (1.39)	48.6	42.2	67.6	56.3	29.4	39.7
Majuro	243	2.94 (1.35)	44.8	35.7	63.3	47.4	19.1	32.4
Namu	96	2.94 (1.35)	53.1	38.5	46.9	82.3	32.3	40.6
Utrik	48	2.94 (1.46)	56.2	25.5	45.8	46.1	18.4	25.6
Wotje	70	3.38 (1.43)	51.4	21.4	50.0	44.3	12.9	24.3
Total	919	3.09 (1.30)	48.5	36.4	59.9	53.5	23.8	33.2

* Defined as hemoglobin < 110 g/L. Hemoglobin not measured in Arno, Kwajalein, Majuro, and Utrik among one, eight, five, and one subjects, respectively.
† Defined as serum vitamin A < 0.70 μM/L.
‡ Defined as serum ferritin < 12 μg/L. Serum ferritin not measured in Ailuk, Arno, Enewetak, Kwajalein, Majro, and Utrik among 16, 25, 1, 7, 30, and 9 subjects, respectively.
§ Defined as serum ferritin < 12 μg/L and hemoglobin < 110 g/L.
SD, standard deviation

mately 20% of the entire population of children ages 1 to 5 y living the Republic of the Marshall Islands.[9] The sampling strategy for the study was based on the 1988 census of the Republic of the Marshall Islands, which provided data on the average number of children of the target age group within each household, determined by dividing the number of children in a locality by the number of households in the same location. This number was then divided into the number of children to be sampled to obtain the number of households to be visited. Households to be visited were chosen by systematic sampling of every fifth household. When available, the birth dates of the children were ascertained from the children's health cards; otherwise, the birth dates were obtained by asking the parent or guardian. The survey team consisted of at least one Marshallese-speaking health care worker, a phlebotomist, and a medical doctor. Oral informed consent was obtained from a parent or guardian before participation in the survey as considered appropriate by the institutional review board for this setting. The Ministry of Health and Environment of the Republic of the Marshall Islands supported the project and assisted with the planning and development of this evaluation.

Blood samples (2 mL) were obtained by venipuncture. Hemoglobin was measured with a hemoglobinometer (HemoCue, Mission Viejo, CA, USA). Venous blood samples were wrapped immediately in aluminum foil and stored at 4°C until centrifugation (200*g*, 10 min, room temperature) in a local laboratory. Aliquots of serum were made in cryovials, and samples were placed immediately in liquid nitrogen. Serum samples were kept in liquid nitrogen or at −70°C until the time of laboratory analyses, which were conducted in 1999 and 2002. Retinol and ferritin remain stable at −70°C for 20 y or more.[10] Serum retinol was measured in 919 children by using reverse-phase high-performance liquid chromatography, as described elsewhere.[9] Serum ferritin concentrations were measured with enzyme-linked immunosorbent assay (Human Ferritin Enzyme Immunoassay Test Kit, American Laboratory Products Company, Windham, NH, USA). Pooled human standards were used to measure intra- and interassay coefficients of variation in laboratory analyses. For serum retinol measured in 919 children, the within-assay and between-assay coefficients of variation were 3% and 8%, respectively. For serum ferritin measured in 831 children, the within-assay and between-assay coefficients of variation were 6.7% and 20.3%, respectively. The study protocol was approved by the institutional review board of the Pacific Health Research Institute of Hawaii and the Ministry of Health of the Republic of the Marshall Islands.

Groups were compared with Student's *t* test for continuous variables where appropriate, and categorical variables were compared with χ^2 or exact tests.[11] Anemia was defined as a hemoglobin level below 110 g/L.[12] Vitamin A deficiency was defined as moderate (serum retinol < 0.70 μM/L) and severe (serum retinol < 0.35 μM/L).[13] Iron deficiency was defined as a serum ferritin concentration below 12 μg/L, and iron deficiency anemia was defined as a serum ferritin concentration below 12 μg/L and a hemoglobin concentration below 110 g/L.[12] Spearman's correlation was used to examine correlation between hemoglobin and serum retinol concentrations.[11]

RESULTS

The mean (± standard deviation) age of children in the study was 3.1 ± 1.3 y, and 48.6% of the children were female. The proportion of children who had serum vitamin A concentrations below 0.70 μM/L was 59.9%. Of 904 children who had hemoglobin concentrations measured, 36.4% were anemic. Of 831 children who had serum ferritin concentrations measured, 53.5% had iron deficiency and 23.8% had iron deficiency anemia. Serum ferritin was not measured in 88 children because of inadequate sample volume; these children did not differ significantly by age, sex, and retinol level from the 831 children who had a ferritin measurement (data not shown). The prevalence of vitamin A deficiency, anemia, iron deficiency, iron deficiency anemia, and iron and vitamin A deficiencies combined is shown by atoll in Table I. The atolls that appeared to have the highest prevalence of vitamin A deficiency were Arno, Majuro, and Kwajalein. The atoll that appeared to have the highest prevalence of iron deficiency was Namu.

The frequency distribution of serum retinol concentrations is shown in Figure 1. Mean (± standard deviation) retinol concentrations among boys and girls were 0.64 ± 0.29 and 0.68 ± 0.28 μM/L, respectively ($P = 0.033$). The mean (± standard deviation)

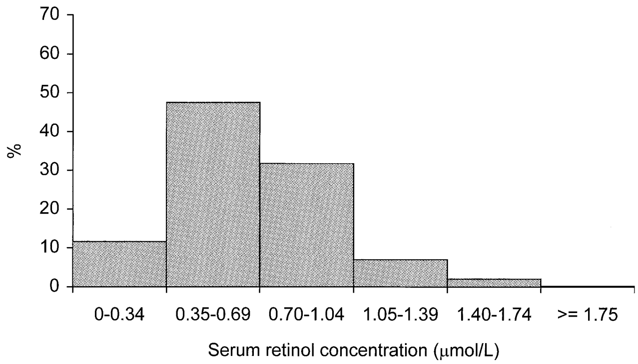

FIG. 1. Frequency distribution of serum retinol concentrations in 919 preschool children in the Republic of the Marshall Islands.

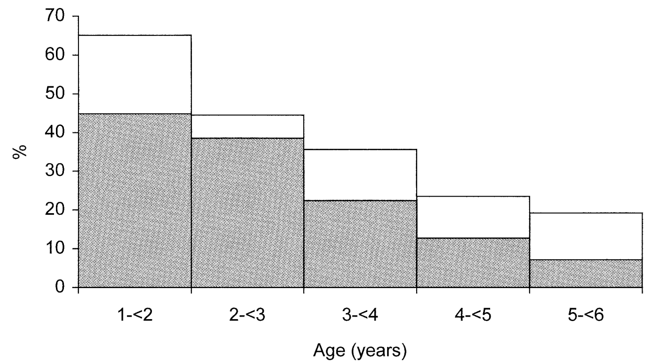

FIG. 3. Prevalence of anemia by age. Prevalence of children with anemia decreased with age ($P < 0.0001$). Shaded regions indicate proportions of children who had iron deficiency anemia (serum ferritin < 12 μg/L). Prevalence of children with iron deficiency anemia decreased with age ($P < 0.0001$).

ages of preschool children who were deficient in vitamin A (serum retinol < 0.70 μM/L) and non-deficient were 3.2 ± 1.4 and 2.9 ± 1.5 y, respectively ($P = 0.01$). The proportions of children with serum retinol concentrations consistent with moderate and severe vitamin A deficiency are shown by age in Figure 2. There appeared to be a trend toward an increase in the proportion of children with moderate vitamin A deficiency but not with severe vitamin A deficiency by advancing age ($P = 0.011$ and 0.21, respectively).

The prevalences of anemia and iron deficiency by age are shown in Figure 3. Mean (± standard deviation) hemoglobin concentrations among boys and girls were 110 ± 10 and 110 ± 9 g/L, respectively ($P = 0.74$). The mean (± standard deviation) ages of children with and without anemia were 2.5 ± 1.3 and 3.4 ± 1.3 y, respectively ($P < 0.0001$). The mean ages of children with and without iron deficiency anemia were 2.3 ± 1.2 and 3.4 ± 1.4 y, respectively ($P < 0.0001$). There was a significant downward trend in the prevalences of iron deficiency and iron deficiency anemia by advancing age ($P < 0.0001$ for both). The overall prevalences of vitamin A deficiency, iron deficiency, and combined vitamin A and iron deficiencies were 59.9%, 53.5%, and 33.2%. Serum retinol and hemoglobin concentrations were correlated ($n = 904$; Spearman's correlation, $r = 0.159$; $P < 0.0001$). Vitamin A deficiency was associated with anemia (Table II; $P = 0.0095$).

DISCUSSION

The present study showed that the prevalence of vitamin A deficiency is extremely high, occurring in about 60% of preschool children in the Republic of the Marshall Islands. These data are consistent with recent epidemiologic studies showing an extremely high prevalence of vitamin A deficiency among preschool children in the South and Western Pacific regions.[6] In other epidemiologic studies conducted in the region, low consumption of vitamin A–rich foods, lack of home gardening, and low levels of maternal education have been identified as risk factors for clinical vitamin A deficiency.[14,15] Mean serum concentrations of vitamin A were lower among boys than among girls, which corroborated a general finding that has been described among many different populations in developing countries.[6]

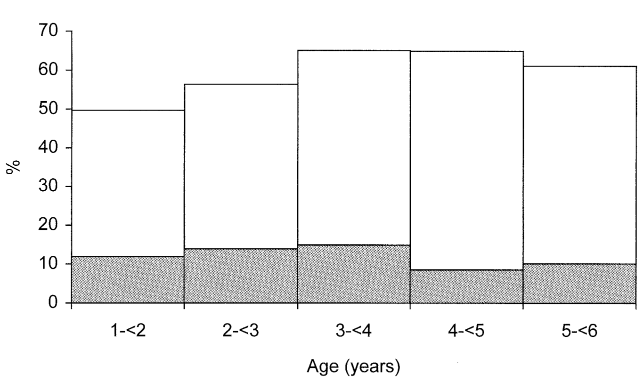

FIG. 2. Prevalence of vitamin A deficiency (serum retinol < 0.70 μM/L) by age. Prevalence of children with serum retinol below 0.70 μM/L increased with age ($P = 0.011$). Shaded regions indicate proportions of children who had serum retinol below 0.35 μM/L. Prevalence of children with serum retinol below 0.35 μM/L did not appear to increase with age ($P = 0.21$).

Worldwide there are limited data available regarding the prevalence of anemia among preschool children, and prevalence estimates of the World Health Organization (WHO) Global Database on Anemia are largely based on data from surveys conducted in North America and Latin America.[16] In other recent studies, the prevalences of anemia, also defined as hemoglobin concentrations below 110 g/L, were 30% in Honduras among children ages 12 to 71 mo[17] and about 41% in Pernambuco State, Brazil among children ages 6 to 59 mo.[18] The 36.4% prevalence of anemia among preschool children in the Republic of the Marshall Islands is somewhat lower than the estimated 42% prevalence among preschool children in developing countries according to the WHO Global Database on Anemia.[16]

Nearly half the children in the study had iron deficiency and about one-fourth had iron deficiency anemia. Iron deficiency in this study was based on serum ferritin concentrations, and because serum ferritin is a positive acute phase reactant, this laboratory test may have underestimated the proportion of children with iron deficiency in a population with a high prevalence of infections. Thus, an important limitation of this study is that the prevalence of iron deficiency as measured by serum ferritin likely was a conser-

TABLE II.

VITAMIN A DEFICIENCY AND ANEMIA*

	Vitamin A Deficiency†	
Anemia‡	No ($n = 361$)	Yes ($n = 543$)
No ($n = 575$)	248 (27.6%)	327 (36.0%)
Yes ($n = 329$)	113 (12.5%)	216 (23.9%)

* By χ^2 test, $P = 0.0095$.
† Defined as serum vitamin A < 0.70 μM/L.
‡ Defined as hemoglobin < 110 g/L.

vative estimate. The etiology of iron deficiency was not investigated in the present study, but the main factors contributing to iron deficiency among these children likely include a low intake of dietary iron and hookworm infection. The best sources of iron are meat, fish, and poultry because the heme iron contained in these foods have high bioavailability,[19] but these food sources also tend to be the most expensive types of food. Hookworm infection is a major cause of anemia in tropical and subtropical areas throughout the world.[20] Hookworm infection and anemia have been described among children in Kiribati (formerly known as the Gilbert Islands), an adjacent archipelago that lies to the south of the Republic of the Marshall Islands.[21]

Although there is much recent interest in identifying multiple micronutrient deficiencies among preschool children in developing countries, there have been few population-based surveys describing iron deficiency and vitamin A deficiency in the same children.[8] Vitamin A deficiency and iron deficiency were common among Marshallese children, and about one-third of these children had vitamin A and iron deficiencies. Although iron deficiency was more prevalent among younger preschool children and vitamin A deficiency was prevalent among older preschool children in this survey, these data suggested that there is a large group of children at risk of having the co-occurrence of both deficiencies. Thus, the present study in the Republic of the Marshall Islands and a recent study in Honduras[8] suggested that nutritional interventions that are targeted to one micronutrient will miss a substantial proportion of children who have the other deficiency.

In this study, serum retinol concentrations were positively correlated with hemoglobin concentrations, an observation that corroborated previous studies.[3] Several intervention studies have associated vitamin A supplementation with an increase in hemoglobin concentrations.[22–28] Potential mechanisms by which vitamin A supplementation may contribute to reducing anemia include mobilization of iron stores from the liver, enhanced erythropoiesis, and the reduction of the infections and the accompanying anemia of infection.[3]

The current study raised the possibility that the prevalence of anemia may be increasing among preschool children in the Republic of the Marshall Islands. In a previous survey conducted in the 1980s among 563 Marshallese children, the prevalence of anemia, defined as a hemoglobin concentration below 110 g/L, was 8.6% among children ages 1 to 5 y.[29] The previous survey was conducted on Utrik, Kwajalein, Majuro, and Rongelap atolls, and overlapped with the present study that covered the same atolls except for Rongelap. In the past two or three decades, there have been rapid changes in the diets of people living in the South Pacific, with replacement of traditional foods with highly processed foods of low nutritional value.[6] A limitation of this study is that dietary assessment was not conducted, which may provide some insight into the issue of diet among Marshallese children. The same changes that have accompanied the emergence of vitamin A deficiency as a public health problem in the Republic of the Marshall Islands also may be at play in the apparent increase in anemia among these preschool children. Since the time of the survey in 1994 and 1995, the Ministry of Health of the Republic of the Marshall Islands has initiated a countrywide vitamin A capsule distribution program, but at the present time there is no program for addressing iron deficiency and iron deficiency anemia.

ACKNOWLEDGMENTS

The authors thank the health care workers in the Republic of the Marshall Islands, especially Laling Riklon, Grace Heine, Kenya Amles, and Ailon Moses, for their diligent assistance, and Dana Totin for her assistance in interpretation of the data.

REFERENCES

1. Micronutrient Initiative/UNICEF/Tulane. *Progress in controlling vitamin A deficiency.* Ottawa: Micronutrient Initiative, 1998
2. McLaren DS, Frigg M. *Sight and life manual on vitamin A deficiency disorders (VADD)*, 2nd ed. Basel: Task Force Sight and Life, 2001
3. Semba RD, Bloem MW. The anemia of vitamin A deficiency: epidemiology and pathogenesis. Eur J Clin Nutr 2002;56:271
4. Yip R. Iron deficiency and anemia. In: Semba RD, Bloem MW, eds. *Nutrition and health in developing countries.* Totowa, NJ: Humana Press, 2001:327
5. Lozoff B, Wachs TD. Functional correlates of nutritional anemias in infancy and early childhood—child development and behavior. In: Ramakrishnan U, ed. *Nutritional anemias.* Boca Raton: CRC Press, 2001:69
6. Semba RD, Palafox NA. Prevention of nutritional blindness in the South Pacific. Asia Pac J Ophthalmol 2002;14:6
7. Flores EG. *Report of the national nutrition survey of the Republic of the Marshall Islands.* New York: UNICEF, 1991
8. Albalak R, Ramakrishnan U, Stein AD, et al. Co-occurrence of nutrition problems in Honduran children. J Nutr 2000;130:2271
9. Gamble MV, Ramakrishnan R, Palafox NA, et al. Retinol binding protein as a surrogate measure for serum retinol: studies in vitamin A–deficient children from the Republic of the Marshall Islands. Am J Clin Nutr 2001;73:594
10. Comstock GW, Alberg AJ, Helzlsouer KJ. Reports effects of long-term freezer storage on concentrations of retinol, beta-carotene, and alpha-tocopherol in serum or plasma summarized. Clin Chem 1993;39:1075
11. Rosner B. *Fundamentals of biostatistics,* 2nd ed. Boston: Duxbury Press, 1986
12. WHO/UNICEF/UNU. *Iron deficiency: indicators for assessment and strategies for prevention.* Geneva: World Health Organization, 1997
13. West KP Jr, Darnton-Hill I. Vitamin A deficiency. In: Semba RD, Bloem MW, eds. *Nutrition and health in developing countries.* Totowa, NJ: Humana Press, 2001:267
14. Centers for Disease Control and Prevention. Vitamin A deficiency among children—Federated States of Micronesia, 2000. MMWR 2001;50:509
15. Schaumberg DA, O'Connor J, Semba RD. Risk factors for xerophthalmia in the Republic of Kiribati. Eur J Clin Nutr 1996;50:761
16. Administrative Committee on Coordination/Sub-Committee on Nutrition. *Fourth report on the world nutrition situation.* Geneva: Administrative Committee on Coordination/Sub-Committee on Nutrition, 2000
17. Nestel P, Melara A, Rosado J, Mora JO. Vitamin A deficiency and anemia among children 12–71 months old in Honduras. Rev Panam Salud Publica 1999;6:34
18. Osorio MM, Lira PI, Batista-Filho M, Ashworth A. Prevalence of anemia in children 6–59 months old in the state of Pernambuco, Brazil. Rev Panam Salud Publica 2001;10:101
19. Allen L, Casterline-Sabel J. Prevalence and causes of nutritional anemias. In: Ramakrishnan U, ed. *Nutritional anemias.* Boca Raton: CRC Press, 2001:7
20. Pawlowski ZS, Schad GA, Stott GJ. *Hookworm infection and anaemia: approaches to prevention and control.* Geneva: World Health Organization, 1991
21. Roberts AB, Roberts P, Tira T, Tulimanu K. Malnutrition and anaemia in Gilbertese pre-school children: a case-finding and epidemiological survey. J Trop Pediatr 1981;27:78
22. Muhilal, Permeisih D, Idjradinata YR, Muherdiyantiningsih, Karyadi D. Vitamin A-fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. Am J Clin Nutr 1988;48:1271
23. Mejía LA, Chew F. Hematological effect of supplementing anemic children with vitamin A alone and in combination with iron. Am J Clin Nutr 1988;48:595
24. Semba RD, Muhilal, West KP Jr, et al. Impact of vitamin A supplementation on hematological indicators of iron metabolism and protein status in children. Nutr Res 1992;12:469
25. Suharno D, West CE, Muhilal, Karyadi D, Hautvast GAJ. Supplementation with vitamin A and iron for nutritional anaemia in pregnant women in West Java, Indonesia. Lancet 1993;342:1325
26. Mwanri L, Worsley A, Ryan P, Masika J. Supplemental vitamin A improves anemia and growth in anemic school children in Tanzania. J Nutr 2000;130:2691
27. Muslimatun S, Schmidt MK, Schultink W, et al. Weekly supplementation with iron and vitamin A during pregnancy increases hemoglobin concentration but decreases serum ferritin concentration in Indonesian pregnant women. J Nutr 2001;131:85
28. Kumwenda N, Miotti PG, Taha TE, et al. Antenatal vitamin A supplementation increases birth weight and decreases anemia among infants born to human immunodeficiency virus–infected women in Malawi. Clin Infect Dis 2002;35:618
29. Dungy CI, Morgan BC, Heotis PM, Branson HE, Adams WH. Normal hematologic values and prevalence of anemia in children living on selected Pacific atolls. Acta Haematol 1987;77:95

(For an additional perspective, see Editorial Opinions.)