

Articles

Delayed Bottle Weaning and Iron Deficiency in Southeast Asian Toddlers

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We undertook this study to determine if culturally influenced feeding practices are associated with iron deficiency in infants and toddlers from low-income families. We obtained a dietary survey, illness history, hematocrit, and zinc protoporphyrin-to-heme ratio (ZPP/H) from 35 Southeast Asian children and 73 children of other ethnicities between ages 5 and 30 months. We confirmed iron deficiency by serum ferritin measurement in children with ZPP/H >80 mmol/mol or evaluated them after a 3-month iron treatment. Sixty percent of the Southeast Asian children had elevated ZPP/H ratios, compared with 14% of children of other ethnicities. Follow-up studies confirmed iron deficiency in 12 of 21 Southeast Asian children with elevated ZPP/H; 75% (eight) of those with confirmed iron deficiency were 24 to 30 months of age. We found that toddler feeding practices differ between Southeast Asians and other ethnic groups. All 17 Southeast Asian toddlers were still bottle fed at their second birthday, compared with 10 of 21 same-age children of other ethnicities. Persistence of bottle feeding after 2 years of age was highly associated with elevation of ZPP/H in Southeast Asian children but not in other children. Clinicians need to be aware of this problem and carefully monitor iron status in children not weaned from the baby bottle by age 2 years. Changes in education practices and policies are needed to prevent iron deficiency from the overintake of cow's milk that results from prolonged bottle feedings in this ethnic group.

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With the increased use in the US of iron supplements with breastfeeding and iron-fortified formulas, the prevalence of iron deficiency in children younger than 1 year has decreased.^{1,2} Because of its impact on the psychomotor development of children, however, iron deficiency does remain a significant concern.^{3,4} In Seattle's Harborview Medical Center, an urban clinic in a city with a large Southeast Asian immigrant population, we have seen many Southeast Asian toddlers with severe iron-deficiency anemia. The following case illustrates the problem.

A 27-month-old Southeast Asian child, whose caregiver complained of poor solid food intake for 3 months, was brought in with pallor and stomachaches. The child was consuming large amounts of whole milk from a baby bottle. Physical examination was normal except for marked pallor. Hematocrit was 15%, Hb 3.8 g/dL, MCV <50 fL; blood smear showed marked microcytosis and hypochromia; zinc protoporphyrin-to-heme ratio

(ZPP/H) was 454 mmol/mol (normal ≤ 80 $\mu\text{mol/mol}$); and G6PD screen was negative. Chart review showed normal hemoglobin electrophoresis. At 14 months of age, soon after being changed from an iron fortified formula to whole milk, the hematocrit had been 34% and the ZPP/H ratio 53 mmol/mol. After 2 months of oral iron therapy and decreasing the whole milk intake to 8 ounces a day, the child's hematocrit returned to 33%.

Cases such as this led us to conduct a screening study among a multiethnic population of young children to determine the incidence of iron deficiency in different ethnic groups (Carlson TH, Graham EA, unpublished data, 1997). The investigation in this current report was conducted to determine if culturally influenced feeding practices were associated with the high prevalence of iron deficiency in Southeast Asian toddlers found in the first study.

ZPP/H was the index used since it detects altered iron metabolism at an early stage of iron deficiency before

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ABBREVIATIONS USED IN TEXT

ZPP/H = zinc protoporphyrin-to-heme ratio
 WIC = Special Supplemental Food Program for Women,
 Infants and Children

anemia appears and can be done on the small amount of blood cells left over after the hematocrit determination.⁵ Protoporphyrin normally combines with either iron or zinc in erythropoiesis to produce heme or zinc protoporphyrin. If iron availability is limited, the level of zinc protoporphyrin increases.

Methods

The study subjects (Table 1) consisted of 108 children between the ages of 5 and 30 months, seen consecutively at their regular visits to the WIC Program (Special Supplemental Food Program for Women, Infants and Children) during a 5-month period between October 1991 and March 1992. Information obtained included age, sex, ethnicity, length of enrollment in WIC, feeding practices during the first year of life, history of febrile illness lasting >24 hours in the previous week, and treatment with oral iron in the previous 3 months. In addition, for toddlers (≥ 2 years of age), parents were asked if weaning from the baby bottle had occurred at the time of the visit, and if so, at what age. Charts of all children with elevated ZPP/H were reviewed for number of illness visits in the 3 months before the WIC visit and prior hematologic evaluation or iron treatment. The study was approved by the University of Washington Human Subjects Review Committee.

All families met the low-income guidelines to qualify for the WIC program. Thirty-five children were first- or second-generation Southeast Asians, primarily from Laos and Cambodia, and 73 children were classified as "other," including 29 African and African-American, 18 European-American, eight Hispanic, and 18 mixed-ethnicity children.

Centrifuged micro-hematocrits were determined

from capillary blood samples according to WIC program requirements. The same specimens were subjected to ZPP/H ratio analysis using the ProtoFluor-Z hematofluorometry system (Helena Laboratories, Beaumont, TX).⁶ Children treated with iron as the result of an abnormal ZPP/H ratio ($>80 \mu\text{mol/mol}$) had hemoglobin, hematocrit, and red blood cell indexes determined by Coulter analysis. When possible, serum ferritin concentration (Stratus Fluorometric System, Baxter Healthcare, Miami, FL) was determined before iron treatment. After 3 months of oral iron treatment (5–6 mg elemental iron/kg body weight per day), Coulter analyses and ZPP/H tests were repeated.

All laboratory tests were monitored by an internal quality control program and by proficiency testing programs administered by the College of American Pathologists or other recognized proficiency testing programs. To avoid interference from bilirubin or other contaminants, specimens with ZPP/H $>80 \mu\text{mol/mol}$ underwent a repeat ZPP/H analysis on washed red blood cells. The repeat measurement was reported as the final ZPP/H level.

Data were analyzed using the RS/1 statistical package (BBN Software Products, Cambridge, MA) or StatView II (Abacus Concepts, Berkeley, CA). The two-tailed Student's *t* test was used to compare the mean ZPP/H levels of Southeast Asian children and children of other ethnicities. The nonparametric Mann-Whitney test was used to compare mean ZPP/H by age groups and by weaning status in 2-year-old children.

Results

Southeast Asian children had a mean ZPP/H that was significantly higher than the mean for children of other ethnicities (108 vs 65 $\mu\text{mol/mol}$; $P < 0.0001$), but mean hematocrit values for Southeast Asian children were slightly higher than those of the other children ($35 \pm 3\%$ vs $34 \pm 2\%$; $P < 0.01$). Two-thirds of the children with ZPP/H $>80 \mu\text{mol/mol}$ were Southeast Asian, as were 10 of the 11 children with ZPP/H $>120 \mu\text{mol/mol}$. Overall,

TABLE 1.—Characteristics of Study Children, Ages 5–30 Months, Seen in WIC Clinic for Routine Nutrition Assessment and Hematocrits

	Total (n = 108)	Southeast Asian (n = 35)	Other* (n = 73)
Age (years)	1.4 \pm 0.8	1.7 \pm 0.8	1.3 \pm 0.7
Months enrolled in WIC	15 \pm 10	20 \pm 10	13 \pm 8
Fraction of life in WIC	0.9 \pm 0.2	1.0 \pm 0.1	0.8 \pm 0.3
Sex (male/female)	60/48	20/15	40/33
Infection in past week	23 (21)	2 (6)	21 (29)
Iron treatment in past 3 months	12 (11)	2 (6)	10 (14)
Type of infant feeding in first year			
Iron-fortified formula	79 (73)	29 (83)	50 (69)
Breastfeeding and formula	25 (23)	4 (11)	21 (29)
Other	4 (4)	2 (6)	2 (3)

Data are means \pm SD or n (%).
 *Including 29 African-American, 18 European-American, eight Hispanic, and 18 mixed-race children.

60% of the Southeast Asian children had elevated ZPP/H vs 14% of all other children.

Southeast Asian children had higher mean ZPP/H at all age levels. In contrast to children of other ethnicities, they showed an increase in ZPP/H from infancy through toddler age. The differences in ZPP/H by age among other children were not significant (Figure 1). Twelve of the 17 Southeast Asian toddlers ≥ 2 years of age had elevated ZPP/H, and this age group made up 57% of all of the Southeast Asian children with elevated ZPP/H. In contrast, only two of the 21 non-Asian 2-year-old toddlers had elevated ZPP/H.

Although similar percentages of Southeast Asian and other children were given iron-fortified formula up to 1 year of age (Table 1), the Southeast Asian children were much more likely to be bottle fed with cow's milk as 2-year-olds. Less than half (10 of 21) of the other children were bottle fed at 2 years of age and only six were still bottle fed at the time of their WIC visit and blood test. All 17 of the Southeast Asian toddlers ≥ 2 years of age were still bottle fed at their second birthday and only four had been weaned from the bottle at the time that their blood was sampled. Bottle feeding continued in spite of strong recommendations by WIC staff to wean by 18 months of age. Persistence of bottle feeding after 2 years of age in Southeast Asian children was highly associated with elevation of ZPP/H (Figure 2). Bottle feeding was not associated with increased mean ZPP/H in the non-Asian children of this age group.

Quantity of cow's milk consumed appeared to be related to the association of prolonged bottle feeding and elevated ZPP/H in Southeast Asian toddlers. Dietary surveys in the records of our sample indicated that some toddlers consumed relatively large amounts of cow's milk, in some cases 1.4 L/day, twice the WIC recommended amount for children this age. In addition, they had low intake of solid foods with significant iron content.

Further evidence suggesting that iron deficiency was a major cause of the elevated ZPP/H values of the Southeast Asian children, especially for the toddler-age group, was provided by complete follow-up studies in 15 children. Six of the 21 children with elevated ZPP/H did not return for follow-up studies (or their studies were incomplete). Twelve of the 15 children with complete follow-up had additional studies indicating iron deficiency, including seven children with pretreatment ferritin levels <12 mg/L; four children with a >10 mg/L (>1 mg/dL) increase in hemoglobin and a $>20\%$ decrease in ZPP/H after 3 months of iron treatment; and one child with a 21% decrease in ZPP/H after 3 months of treatment (normal ZPP/H posttreatment) but no change in the initial normal hematocrit. Nine of the 12 with confirmed iron deficiency were ≥ 24 months of age. Three children were either iron replete based on normal ferritin levels before treatment or showed no response in ZPP/H or hemoglobin concentration after >3 months of iron treatment.

Other causes of elevated zinc protoporphyrin were considered. Lead poisoning, an alternative cause of high ZPP/H, is virtually unknown among children in the

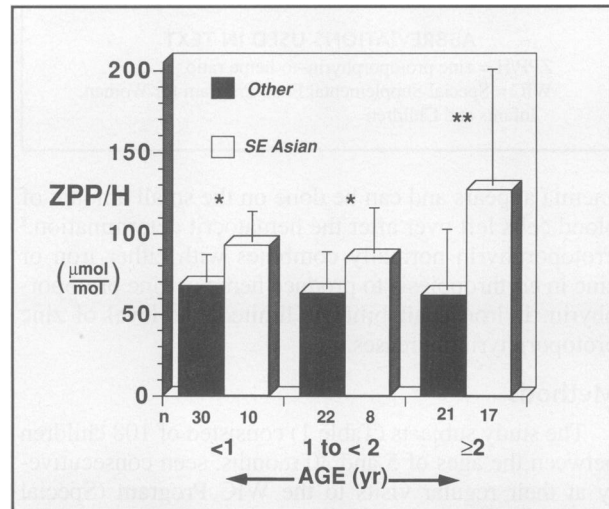


Figure 1.—Effect of age on ZPP/H in children under 3 years of age by ethnic backgrounds. Mean ZPP/H levels in all age groups were higher in Southeast Asian children compared to those of other ethnic backgrounds but was markedly higher for the ≥ 2 year-old group. * indicates $P < 0.05$; ** indicates $P < 0.001$. The number of children in each group is indicated by n. The error bars represent one standard deviation.

Seattle area. Three of the four children with ZPP/H >200 $\mu\text{mol/mol}$ were tested, and all lead levels were <0.39 $\mu\text{mol/L}$ (8 $\mu\text{g/dL}$). Recurrent febrile illness has also been associated with elevated ZPP/H.⁷ Only one Southeast Asian child with elevated ZPP/H was reported to have had a febrile illness in the prior week. Seven of the 21 Southeast Asian children with elevated ZPP/H had a clinic visit for illness in the preceding 3 months, but only one was seen more than once. In contrast, nine of the 10 children of other ethnicities with elevated ZPP/H were seen for illness in the prior 3 months and five were seen two or more times. Parents reported illness in the week prior to blood testing in six of these 10 children.

Discussion

The high prevalence of elevated ZPP/H ratios and iron deficiency in Southeast Asian toddlers in our sample has been observed in other studies in the past decade, although prevalence was not as high as in our sample. These studies did not look at the feeding practices of the children with elevated ZPP/H. A Minnesota household survey found that 22.8% of US-born low-income Southeast Asian children (mean age 1.9 years) had elevated ZPP/H. The majority of those children with elevated ZPP/H had serum ferritin levels <15 mg/L.⁸ A study of Asian children 6 to 36 months of age in Montreal found a higher prevalence of iron deficiency in toddlers—16.5% of 19–36-month-old children were iron deficient compared with 11.4% of 6–12-month-old and 9.9% of 13–18-month-old children.⁹ In contrast, a cross-sectional sample of US children¹⁰ and a longitudinal study of French Canadian children found decreasing iron deficiency in children 2 years and older.¹¹

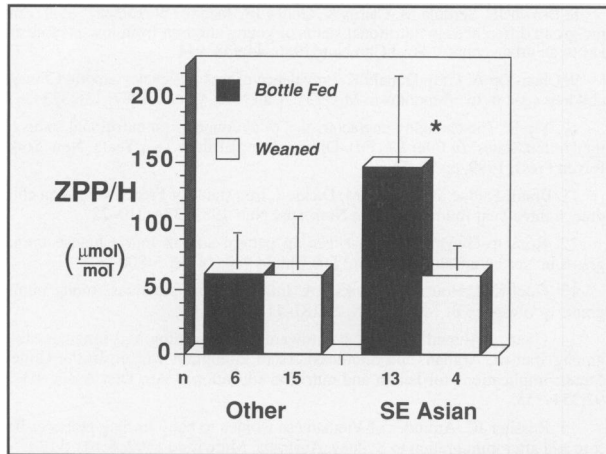


Figure 2.—Influence of weaning on ZPP/H in 2-year-old Southeast Asian children compared to same age children of other ethnic backgrounds. At the time of blood sampling, bottle-fed Southeast Asian children had significantly higher mean ZPP/H levels than bottle-weaned Southeast Asian toddlers. No difference was noted in the mean ZPP/H by type of feeding in children of other ethnicities. * $P < 0.01$. The error bars represent one standard deviation.

From a review of literature and discussions with WIC staff and clinic interpreters, we consider several factors to contribute to the prolonged bottle feeding and excess cow's milk intake in this ethnic group. In Southeast Asia, children are normally breastfed until 2 years of age or until they are displaced from the breast by a new baby. Early weaning from either breast or bottle is not a cultural practice. Studies in the United States and other countries have documented the decline in breastfeeding among Southeast Asian immigrants.¹²⁻¹⁵ Bottle feeding is substituted for breastfeeding and is often continued until 3 or 4 years of age. Southeast Asian children are started on semisolid or solid foods much later than is the practice of other ethnic groups.¹⁶ Families often live in crowded households and place a priority on keeping infants and toddlers from crying or disturbing others. Children are given a bottle when they cry,¹⁷ and it is easier for a toddler to consume large amounts of milk from a bottle than a cup, as use of a cup requires adult supervision. Southeast Asian parenting practices generally put an emphasis on accommodation to infants; gradual change is the rule, so rapid bottle or breast weaning is not culturally acceptable.¹⁵ Finally, the provision of free cow's milk by the WIC program and the lack of iron-containing food selections, except iron-fortified cereals, may encourage the practice of feeding large amounts of milk to toddlers. Unfortunately, culturally acceptable nourishing foods such as rice, noodles, tofu, vegetables, and familiar meats are not provided through the WIC program.

The iron deficiency noted in Southeast Asian toddlers in our study generally had not progressed to anemia at the time of sampling. These children may not be at risk for adverse psychomotor effects if they are weaned from the bottle before anemia develops. Most studies of iron deficiency and child development, however, have

involved children <24 months of age. It is possible that iron deficiency without anemia may have adverse effects on development in children 2 to 3 years of age if it persists for long periods of time without detection and intervention.

The retrospective design of this study is a significant limitation. Although quantity of milk intake was often noted, it was not consistently present in the records. Therefore it was not possible to quantitate cow's milk intake or iron content of solid foods consumed. A quantitative dietary history, obtained prospectively, could provide more detail of cultural differences in infant feeding practices. It is likely that iron deficiency results from the quantity of milk consumed. Similarly, prospectively obtaining venous blood samples on all children at the time of the WIC visit would have provided more precise determination of iron status.

Since conducting this study, we have found that hemoglobinopathies including hemoglobin E, alpha and beta thalassemia trait, are associated with a mild increase in mean ZPP/H in iron-sufficient adults.¹⁸ Such disorders are common in Southeast Asians, with prevalence as high as 40 to 60%.¹⁹ This may explain the findings in our sample of higher mean ZPP/H at all ages in Southeast Asian children compared with those of other ethnicities. This type of population factor, however, would not explain the associations of increased ZPP/H with age and with persistent bottle feeding after age 2 years in Southeast Asian children in our sample.

An important outcome of this study is the demonstration that if hematocrit had been used as the only screening test for iron status, a large fraction of the iron-deficient Southeast Asian children would not have been identified. The ZPP/H, a very sensitive screening test for iron deficiency, provided information about iron status that correlated well with dietary histories. It identified children at risk to develop anemia and allowed for timely and appropriate nutritional intervention.

Conclusions and Implications for Pediatric Practice

1. Cultural influences that prolong bottle feeding past 2 years of age are associated with iron deficiency in Southeast Asian toddlers. Weaning to a cup with increased solid food intake should be encouraged by 18 months of age. Where this is not accomplished, toddlers should be monitored for development of iron deficiency, and oral iron supplements should be provided.

2. The pattern of prolonged bottle feeding in Southeast Asian families does not appear to change in response to current health education approaches encouraging early weaning. Since many of these children are in the WIC program, development of culturally sensitive education approaches and materials by WIC could help encourage earlier weaning. Culturally acceptable food supplement packages for children >1 year of age—providing high-protein foods besides dairy products and foods with substantial amounts of iron and vitamin C (to aid iron absorption)—would also encourage a more

nutritionally adequate diet for these toddlers. Iron fortification of toddler foods should be considered to prevent iron deficiency in spite of prolonged bottle feeding.²⁰

3. Hematocrit is not a sensitive screening test for iron status, especially in the Southeast Asian toddler population because of its high risk for dietary iron deficiency. It is recommended that programs such as WIC use ZPP/H as an inexpensive screening test for iron deficiency in the toddler population.

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