

# Postpartum thiamine deficiency in a Karen displaced population<sup>1-3</sup>

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## ABSTRACT

**Background:** Before its recognition, infantile beriberi was the leading cause of infant death in camps for displaced persons of the Karen ethnic minority on Thailand's western border.

**Objective:** This study aimed to document thiamine status in the peripartum period to examine the current supplementation program and the correlation between the clinical manifestations of thiamine deficiency and a biochemical measure of thiamine status.

**Design:** Women were enrolled prospectively at 30 wk of gestation and were followed up weekly until delivery and at 3 mo postpartum. Thiamine supplementation during pregnancy was based on patient symptoms.

**Results:** At 3 mo postpartum, thiamine deficiency reflected by an erythrocyte transketolase activity (ETKA)  $\geq 1.20\%$  was found in 57.7% (15/26) of mothers, 26.9% (7/26) of whom had severe deficiency (ETKA  $> 1.25\%$ ). No significant associations between ETKA and putative maternal symptoms or use of thiamine supplements were found.

**Conclusions:** Biochemical postpartum thiamine deficiency is still common in Karen refugee women. This situation may be improved by educating lactating women to reduce their consumption of thiaminase-containing foods and by implementing an effective thiamine supplementation program. *Am J Clin Nutr* 2001;74:808-13.

**KEY WORDS** Erythrocyte transketolase activity, lactation, postpartum, pregnancy, refugee, thiamine deficiency, thiamine hydrochloride, Karen ethnic minority, Thailand, women

## INTRODUCTION

Thiamine deficiency is common where highly polished rice is the major staple food (1-4) and where other primary dietary sources of thiamine (meat, fish, and legumes) are in short supply (5). Deficiency is compounded when local diets include foods such as fermented fish (6), tea leaves, and betel nut, which contain antithiamine factors (7, 8). Thiamine deficiency remains an important public health problem in refugee camps on the Thai-Burmese border. Pregnant women and young children are at highest risk of deficiency.

Food and other basic items are provided to the camp's populations by a consortium of charities. The diet in the camps consists largely of polished rice and fermented fish paste. Assessment of the nutritional content of this ration found that it supplies nearly

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adequate energy and protein, but is low in micronutrients, such as vitamin A, vitamin C, folate, and thiamine (9).

Health care in the camps is shared by Médecins sans Frontières (MSF) and the Shoklo Malaria Research Unit (SMRU). The MSF provides most of the health care. For antenatal care and delivery, however, pregnant women attend antenatal clinics at the SMRU, which were established in 1986 (10). The SMRU conducts studies on multidrug-resistant malaria in displaced communities, with a focus on malaria in pregnancy. Women then attend the MSF for postpartum consultations.

At the antenatal clinic of the SMRU, all pregnant women are given a routine supplement of food (4 eggs and 500 g soybeans/wk); if they have clinical signs of beriberi (principally peripheral paresthesia), they are also given an oral thiamine hydrochloride dosage of 100 mg/d until delivery. At the MSF consultations, lactating women are given a routine supplement consisting of the routine food supplement and a single thiamine hydrochloride dosage of 10 mg/wk. These programs were initiated in 1988, when it was recognized that infantile beriberi was a leading cause of infant mortality (11, 12).

All infants presenting to the nearest hospital, the SMRU, or the MSF with acute infantile beriberi receive intramuscular thiamine (50 mg) on admission. Since this program was implemented, infant mortality has decreased significantly from 250 to 78 deaths per 1000 live births from 1988 to 1995 (13).

No detailed surveys of thiamine status have been conducted to document the extent of thiamine deficiency in this population.

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The present prospective study was thus designed to document thiamine status in late pregnancy, to examine the current supplementation program, and to examine the correlation between the clinical manifestations of thiamine deficiency and a biochemical measure of thiamine status.

## SUBJECTS AND METHODS

### Study design

Pregnant women attending the antenatal clinics of the SMRU were enrolled in the study if they gave informed consent and agreed to deliver their infants at the unit. The project was approved by the Karen Ethics Committee and the ethical committee of the Faculty of Tropical Medicine of Mahidol University. The purpose and methods of the survey were explained to all participants in their own language, and participants were free to withdraw from the protocol at any time with no consequences. Women were enrolled at  $\approx 30$  wk of gestation as estimated from fundal height and date of last menstruation. No techniques such as ultrasound for obtaining accurate measurements of gestation were available in the camp.

According to standard antenatal care, women were actively screened verbally each week for any peripheral numbness or limb tingling and were supplemented with oral thiamine hydrochloride (100 mg/d) until delivery if they had these symptoms. Thus, some women had received thiamine by the time they reached 30 wk of gestation and entered the study and hence were included in the supplemented group. The unsupplemented group included women who had not received any thiamine during pregnancy before enrollment. Women in the unsupplemented group who became symptomatic during the course of the study were treated with thiamine and were excluded from analysis, as were women with twins or premature deliveries. Recruitment aimed to include 30 women in the supplemented group and 30 women in the unsupplemented group.

On admission, women were asked about their consumption of thiaminase-containing foods (betel nut, fish paste, and fermented tea leaves). An obstetric and medical history was taken once and examinations that included assessment of fundal height, fetal heart beat, fetal presentation, and maternal weight were performed weekly. A neurologic examination aimed at detecting symptoms and signs of thiamine deficiency was carried out at enrolment and weekly until delivery. A trained Karen midwife assessed the women for muscular weakness (by asking them to perform squats and by asking about cramping or painful muscles), paresthesia (peripheral numbness and tingling or plantar pain), proprioception (hallux position sense), and autonomic dysfunction (postural blood pressure change, anorexia, nausea, or constipation). The maternal neurologic examination was not performed at 3 mo postpartum.

Maternal blood samples were taken at 30 wk, at delivery, and at 3 mo postpartum. Cord blood samples were taken from women who delivered their infants in the unit. Maternal breast-milk samples were collected only at 3 mo postpartum from women who also gave blood samples. Any supplementation with thiamine or vitamin B complex and any use of other medications were documented throughout the pregnancy. All SMRU deliveries were supervised by Karen midwives who used WHO partograms. All neonates were weighed with a scale accurate to 50 g (Salter Weighing Products, Minneapolis), were measured (length, head circumference, and arm circumference), were tested by the

Dubowitz method to estimate gestational age (14), and underwent a modified neurologic examination to assess tone, movement, behavior, and visual and auditory alertness (15). The methods of this test are explained in detail elsewhere, and the assessment has been widely used and the normative range is known (16).

Postnatal consultations were conducted by the MSF. The weekly ration of eggs and beans was the same as the antenatal ration. Postnatal thiamine supplementation was routinely given to all lactating women as a single dosage of 10 mg/wk. The MSF protocol did not involve active clinical screening of lactating women for signs of peripheral numbness or limb tingling. Only if a woman complained spontaneously of peripheral numbness and tingling was she given thiamine hydrochloride (100 mg/d for 7 d).

### Blood and milk sample processing

Blood samples (5 mL) were placed into tubes containing lithium heparin and centrifuged immediately at  $6000 \times g$  for 5 min at room temperature. Red blood cells were then separated without disturbing the buffy coat and placed into cryotubes (1.5 mL), which were immediately stored in liquid nitrogen at  $-70^\circ\text{C}$  until assayed. Breast-milk samples were collected  $\geq 1$  h after the previous breast-feed. Once the baby was attached and sucking, the milk was expressed from the contralateral breast, collected (10 mL) in a plain tube, and placed in a freezer ( $-30^\circ\text{C}$ ) within 5 min of collection.

### Laboratory tests

A semiautomated method (AutoAnalyzer II; Technicon Instruments Corp, Tarrytown, NY) was used to measure the enzymatic production of glyceraldehyde 3-phosphate in hemolysates to assay erythrocyte transketolase activity (ETKA) (17). Thiamine deficiency was defined as follows: normal, ETKA  $< 1.20\%$ ; marginal deficiency, ETKA:  $1.20\text{--}1.25\%$ ; and severe deficiency, ETKA  $> 1.25\%$  (18). Maternal milk samples were analyzed by reversed-phase HPLC after enzymatic digestion of the thiamine derivatives to free thiamine (19) and its oxidation to fluorescent thiochrome (20).

### Statistical analysis

Continuous normally distributed data are presented as means (with SDs and ranges) and nonnormally distributed data as medians (with ranges). Percentages are given for categorical data. Categorical variables were compared by the chi-square test with Yates' correction or by Fisher's exact test. Normally distributed variables were compared by the Student's *t* test and nonnormally distributed variables by the Mann-Whitney *U* test. All statistical analyses were performed by the statistical computing package SPSS for WINDOWS (version 9; SPSS Inc, Chicago).

## RESULTS

From July 1995 to December 1995, 61 pregnant women were recruited into the study. Eleven of the women were excluded from data analysis: 2 who delivered twins, 5 who were initially not taking thiamine but became symptomatic (complained of peripheral numbness and tingling) and were prescribed thiamine before delivery, and 4 who had premature deliveries. Thus, data from 50 women were analyzed: 25 in the supplemented group and 25 in the unsupplemented group. There were no significant differences between the groups on admission (**Table 1**). Two

**TABLE 1**  
Characteristics of women at admission by group<sup>1</sup>

	Supplemented (n = 25)	Unsupplemented (n = 25)
Age (y) <sup>2</sup>	25.1 ± 7.2 (15–42)	24.2 ± 7.1 (16–40)
Height (cm) <sup>2</sup>	150.0 ± 4.4 (141–160)	148.8 ± 5.3 (140–161)
Gravidity <sup>3</sup>	2 (1–12)	2 (1–8)
Parity <sup>3</sup>	1 (0–6)	1 (0–6)
Primigravida [n (%)]	7 (28)	10 (40)
Ethnic group [n (%)]		
Poh Karen	9 (36)	9 (36)
Sgaw Karen	13 (52)	10 (40)
Muslim Karen	3 (12)	5 (20)
Thai Karen	—	1 (4)

<sup>1</sup>There were no significant differences between the groups.<sup>2</sup> $\bar{x} \pm SD$ ; range in parentheses.<sup>3</sup>Median; range in parentheses.

women delivered term babies 1 wk after entry to the study; their results were excluded from analysis at 30 wk.

### Diet

All women received  $\approx 533$  g polished rice/d and 33 g fish paste/d as a standard ration. The energy value of the basic adult ration has been estimated to be 8.0 MJ, or 91.5% of the recommended dietary allowance for energy, protein, and calcium (9). Additionally, pregnant women received 350 g yellow beans and 4 eggs weekly, bringing the daily ration to  $\approx 8.8$  MJ. Overall, 90% (45/50) of the women consumed fermented fish, 86%

(43/50) consumed betel nut, and 31% (15/49) consumed fermented tea leaves. Eighty-six percent of women consumed  $\geq 2$  foods containing thiaminase. No women consumed none of the above-mentioned foods.

### Erythrocyte transketolase activity

The supplemented group received a total median dose of 13 300 mg (range: 4200–21 000 mg) thiamine hydrochloride per pregnancy, corresponding to  $0.9 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ . The ETKA results are summarized in **Table 2**. Samples were obtained for only 26 (52%) women at 3 mo postpartum because of armed attacks on the camps; only 16 of these women provided matched breast-milk samples. The median concentration of thiamine in breast milk did not differ significantly between the supplemented (128  $\mu\text{g/L}$ ; range: 890–155  $\mu\text{g/L}$ ;  $n = 7$ ) and unsupplemented (117  $\mu\text{g/L}$ ; range: 7.6–34.2  $\mu\text{g/L}$ ;  $n = 9$ ) groups and was comparable with the normal range in human breast milk. Dostálova et al (21) reported concentrations of 100–200  $\mu\text{g/L}$  for European mothers, and Saudi mothers were reported to have a mean thiamine content of 270  $\mu\text{g/L}$  for mature breast milk (22).

### Neurologic findings and erythrocyte transketolase activity in pregnant women

The mean number of weekly neurologic examinations performed in each group was similar: 6.8 in the supplemented group and 6.5 in the unsupplemented group. There were no gross manifestations of thiamine deficiency in any of the mothers during the study period. More women in the supplemented group had peripheral numbness and cramping or aching muscles at 30 wk,

**TABLE 2**  
Erythrocyte transketolase activity (ETKA) for women at 30 wk of gestation, at delivery, and at 3 mo postpartum<sup>1</sup>

Group	ETKA <sup>2</sup> %	Thiamine status		
		Normal (ETKA < 1.20%)	Marginal deficiency (ETKA: 1.20–1.25%)	Severe deficiency (ETKA > 1.25%)
		n (%)		
30 wk				
Supplemented (n = 25)	1.11 (1.01–1.39)	16 (64)	4 (16)	5 (20)
Unsupplemented (n = 22)	1.13 (1.00–1.58)	14 (64)	2 (9)	6 (27)
Total (n = 47) <sup>3</sup>	1.12 (1.00–1.58)	30 (64)	6 (13)	11 (23)
Delivery				
Mother				
Supplemented (n = 19)	1.09 (1.00–1.50)	16 (84)	1 (5)	2 (11)
Unsupplemented (n = 18)	1.11 (1.00–1.41)	12 (67)	2 (11)	4 (22)
Total (n = 37) <sup>4</sup>	1.10 (1.00–1.50)	28 (76)	2 (8)	6 (16)
Cord blood				
Supplemented (n = 18)	1.05 (1.00–1.36)	17 (94)	—	1 (6)
Unsupplemented (n = 18)	1.09 (1.00–1.22)	17 (94)	1 (6)	—
Total (n = 36) <sup>4,5</sup>	1.05 (1.00–1.36)	34 (94)	1 (3)	1 (3)
3 mo				
Supplemented (n = 13)	1.18 (1.12–1.35)	7 (54)	4 (31)	2 (15)
Unsupplemented (n = 13)	1.22 (1.11–1.45)	4 (31)	4 (31)	5 (38)
Total (n = 26)	1.22 (1.11–1.45)	11 (42)	8 (31)	7 (27)

<sup>1</sup>No significant differences in the proportion of women with thiamine deficiency were found between the supplemented and unsupplemented groups by use of the chi-square test (or Fisher's exact test). Although the median ETKA was lower at delivery (mother and cord blood) and at 3 mo postpartum, no significant differences were found with use of the Mann-Whitney *U* test for comparison of nonparametric data. Thiamine supplementation was discontinued at delivery.

<sup>2</sup>Median; range in parentheses.<sup>3</sup>Two women delivered term babies < 1 wk after entry so their samples were excluded from the analysis at 30 wk; 1 woman's entry sample was lost.<sup>4</sup>Twelve women delivered at home or in the Thai hospital (cesarean delivery) so no ETKA samples were available; 1 woman delivered in the unit but did not have a sample taken.<sup>5</sup>No cord blood could be collected for 1 woman.

**TABLE 3**  
Women symptomatic by neurologic examination at 30 wk and in the week before delivery

Neurologic sign	30 wk		Before delivery	
	Supplemented (n = 25)	Unsupplemented (n = 23) <sup>1</sup>	Supplemented (n = 24) <sup>2</sup>	Unsupplemented (n = 21) <sup>2</sup>
	n (%)			
Arm numbness or tingling	4 (16)	0	8 (2)	0
Leg numbness or tingling	5 (20)	0 <sup>3</sup>	0	0
Plantar pain	2 (8)	2 (9)	0	0
Position sense	1 (4)	0	0	0
Cramping or aching muscles	7 (28)	1 (4) <sup>4</sup>	0	1 (5)
Burning tongue	2 (8)	2 (9)	3 (12)	1 (5)
Anorexia	0	5 (22) <sup>5</sup>	2 (8)	2 (10)
Nausea	0	0	0	1 (5)
Constipation	1 (4)	1 (4)	2 (8)	1 (5)
Squat	0	0	0	0

<sup>1</sup>Two women delivered term babies <1 wk after entry so their neurologic exam was excluded from the 30-wk results.

<sup>2</sup>Five women had their last neurologic test performed >1 wk before delivery so their results are not included in the delivery results.

<sup>3-5</sup>Significantly different from supplemented (Fisher's exact test): <sup>3</sup> $P = 0.051$ , <sup>4</sup> $P = 0.050$ , <sup>5</sup> $P < 0.05$ .

but this difference was of borderline significance (**Table 3**). Anorexia was more common in the unsupplemented group at 30 wk, but this difference was no longer evident at delivery. Peripheral numbness and tingling and cramping or aching muscles appeared to resolve with thiamine supplementation. There was no correlation of abnormal ETKA and positive neurologic findings at 30 wk or at delivery (data not shown).

#### Neonatal outcomes and cord erythrocyte transketolase activity concentrations

The mean birth weight in this cohort ( $n = 50$ ) was  $2894 \pm 326$  g (range: 2100–3600 g). Four newborns missed their gestational and neurologic examinations and the remainder ( $n = 46$ ) had a mean gestational age of  $39.3 \pm 0.9$  wk (range: 37.3–41.0 wk). Birth weight, estimated gestational age, arm circumference, head circumference, and neonatal length were not significantly different between the supplemented and unsupplemented groups (**Table 4**), nor between those with normal or abnormal ETKA at delivery (data not shown). Most newborns scored optimally on most of the neurologic items. Visual alertness, as tested with a red wool ball, was significantly better in neonates from the supplemented group. However, head lag was significantly worse in the same group. Only 2 infants had high cord blood ETKA; thus, this group was too small for meaningful comparison.

#### DISCUSSION

Biochemical thiamine deficiency is common in Karen women in the postpartum period. As noted previously in Thailand (1, 3), we found no association between deficient concentrations of thiamine and the presence of clinical signs thought to indicate thiamine neuropathy (eg, symptoms such as paresthesia). This lack of association, however, may have been related to the subjective nature of the signs.

The prevalence of apparent thiamine deficiency at term in Karen pregnant women is comparable with that reported in previous investigations: 22% in Mexican women (23), 25–30% in Dutch mothers (24), and 20% (1) and 42% (3) in Thai women. Thiamine is probably being redistributed (25, 26) rather than being truly deficient because the cobalamins, stores of which are

normally sufficient for several years, are also affected (27). Preferential delivery to the fetus at the expense of the mother was shown previously (28–32), but the sample size was too small to find the association between thiamine deficiency and intrauterine growth retardation (33–36).

After parturition, maternal serum thiamine concentrations normally increase rapidly (7). The biochemical thiamine deficiency found at 3 mo postpartum in this study probably resulted from the burden of lactation and partly because of the cessation of the large, weekly oral thiamine supplements; postpartum, the supplementation amount dropped from 700 to 10 mg/wk. This peak of abnormal ETKA corresponds to the peak presentation time for infantile beriberi, ie, 3–4 mo (14). No deficiency of breast-milk thiamine concentrations was detected despite the red blood cell biochemical deficiency, suggesting preferential delivery of thiamine to the milk at the expense of the mother.

The main staple of polished rice (36  $\mu\text{g}/\text{MJ}$ ) eaten without adequate supplementation is liable to induce thiamine deficiency, and foods rich in thiamine (pulses and cereals, which contain 290  $\mu\text{g}/\text{MJ}$ , and fruit, vegetables, and meat, which contain 60  $\mu\text{g}/\text{MJ}$ ) are in short supply in the camps (37). Thiamine fortification of rice in the refugee camps or a return to traditional brown rice could be implemented; however, brown rice would

**TABLE 4**

Birth indexes and selected neurologic scores of newborns by group

Clinical and neurologic indexes	Supplemented (n = 23)	Unsupplemented (n = 23)
Birth weight (g) <sup>1,2</sup>	2884 $\pm$ 351	2904 $\pm$ 305
Gestation age (wk) <sup>1</sup>	39.35 $\pm$ 0.88	39.27 $\pm$ 0.98
Length (cm) <sup>1</sup>	47.8 $\pm$ 2.5	47.0 $\pm$ 1.7
Head circumference (cm) <sup>1</sup>	32.2 $\pm$ 2.9	32.1 $\pm$ 2.1
Arm circumference (cm) <sup>1</sup>	10.0 $\pm$ 1.0	10.0 $\pm$ 0.7
Visual alertness score <sup>3</sup>	2 (1–3)	1 (1–4) <sup>4</sup>
Head lag score <sup>3</sup>	2 (2–3)	2 (2–4) <sup>4</sup>

<sup>1</sup> $\bar{x} \pm \text{SD}$ .

<sup>2</sup>Data available for 50 infants.


<sup>3</sup>Median; range in parentheses.

<sup>4</sup>Significantly different from unsupplemented,  $P < 0.05$  (Mann-Whitney  $U$  test).

cause fuel problems because it takes longer to cook and, ironically, it is not liked because it is seen as the food of the poor and least developed.

Foods such as betel nut, fermented fish (fish paste), and tea leaves have high concentrations of antithiamine factors such as thermolabile thiaminase I, of which 1000 U can cause thiamine deficiency in rats within 10 d (38). Supplementation with 110 mg thiamine/d can reduce the effect of raw fermented fish consumption on thiamine degradation but was not sufficient to neutralize the effect of betel nut chewing (8). A simple health measure in this population, where betel nut chewing is common (86%), is education to decrease betel nut intake during pregnancy. Thiaminase-containing foods and thiamine supplements may interact, which may partly explain the absence of correlation found between thiamine supplementation and final ETKA at delivery in this cohort. The fat-soluble thiamine derivatives thiamine propyl disulfide and thiamine tetrahydrofurfural disulfide, are minimally decomposed by thiaminases and could be used to prevent disease in lactating women in this setting (38).

The effect of antenatal thiamine supplementation on the performance of neonates on 2 of the neurologic items requires confirmation elsewhere. No studies have detailed the neurologic condition of newborns of thiamine-deficient mothers, but studies in pregnant rats fed a thiamine-deficient diet showed the offspring's brains to have less phospholipid, cerebrosides, and cholesterol and a lower brain weight compared with the brains of offspring of rats fed a normal diet (39). Postpartum rehabilitation of the infant rats with thiamine still resulted in a lower brain cerebroside content than in the controls, suggesting that early thiamine deprivation may have effects that cannot respond to later therapy.

In conclusion, a biochemical thiamine deficiency exists in postpartum women in this population. The high use of thiaminase-containing foods and the borderline nature of the ration given in the camps supports the need for an effective thiamine supplement in this population. Animal studies suggest profound effects of thiamine deficiency on the developing brain, and the effects on these infants need further assessment. 

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