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Breast Milk Iodine and Perchlorate Concentrations in Lactating Boston-Area Women

Elizabeth N. Pearce, Angela M. Leung, Benjamin C. Blount, Hamid R. Bazrafshan, Xuemei He, Sam Pino, Liza Valentin-Blasini, and Lewis E. Braverman

Section of Endocrinology, Diabetes, and Nutrition (E.N.P., A.M.L., X.H., S.P., L.E.B.), Boston Medical Center and Boston University School of Medicine, Boston, Massachusetts 02118; Division of Laboratory Sciences (B.C.B., L.V.-B.), National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia 30333; and Department of Medicine (H.R.B.), Golestan University Medical School, Golestan, Islamic Republic of Iran

Context: Breastfed infants rely on adequate maternal dietary iodine intake.

Objective: Our objective was to measure breast milk iodine and perchlorate, an inhibitor of iodide transport into the thyroid and potentially into breast milk, in Boston-area women.

Participants: The study included 57 lactating healthy volunteers in the Boston area.

Measurements: Breast milk iodine and perchlorate concentrations and urine iodine, perchlorate, and cotinine concentrations were measured. For comparison, iodine and perchlorate levels in infant formulae were also measured.

Results: Median breast milk iodine content in 57 samples was 155 μg/liter (range, 2.7–1968 μg/liter). Median urine iodine was 114 μg/liter (range, 25–920 μg/liter). Perchlorate was detectable in all 49 breast milk samples (range, 1.3–411 μg/liter), all 56 urine samples (range, 0.37–127 μg/liter), and all 17 infant formula samples (range, 0.22–4.1 μg/liter) measured. Breast milk iodine content was significantly correlated with urinary iodine per gram creatinine and urinary cotinine but was not significantly correlated with breast milk or urinary perchlorate.

Conclusions: Perchlorate exposure was not significantly correlated with breast milk iodine concentrations. Perchlorate was detectable in infant formula but at lower levels than in breast milk. Forty-seven percent of women sampled may have been providing breast milk with insufficient iodine to meet infants' requirements. (***J Clin Endocrinol Metab* 92: 1673–1677, 2007**)

THYROID HORMONE, REQUIRING adequate iodine intake, is critical for neurodevelopment *in utero* and in early life. Worldwide, iodine deficiency remains the leading cause of preventable mental retardation (1). Since the 1920s, U.S. dietary iodine has generally been adequate. However, among U.S. women of childbearing age (15–44 yr), median urinary iodine levels, a biomarker for dietary iodine, decreased by over 50% from 1971–1994 according to data from the National Health and Nutrition Examination Survey (NHANES) (2). More recent NHANES data indicate that urinary iodine levels have stabilized (3). Although the latest NHANES study demonstrated an adequate median urinary iodine level of 167.8 μg/liter in U.S. adults, 16.8% of U.S. women of childbearing age had urinary iodine concentrations of less than 50 μg/liter (3). In our population at Boston Medical Center, we have reported that 9% of 100 women sampled had urinary iodine levels below 50 μg/liter, and 49% had values below that recommended for pregnant women (4). Breastfed infants are reliant on adequate maternal dietary iodine intake (5). The Institute of Medicine's recommended dietary allowance for lactating women is 290 μg iodine daily (6). Based on concerns about adequate iodine intake in the perinatal period, the National Academy of Sciences recently recommended that consideration be given to adding iodine to all prenatal vitamins (7). The American Thyroid Association has also recently recommended that all women receive 150 μg iodine supplements daily during pregnancy and lactation and that all prenatal vitamins contain 150 μg iodine (8).

Perchlorate is an anion that decreases the uptake of iodine into the thyroid gland and potentially into milk ducts in the lactating breast by competitively inhibiting the sodium/iodide symporter (NIS) on the basolateral surface of thyroid cells and on lactating breast cells. Perchlorate is a component of solid rocket fuel, is found in Chilean nitrate fertilizers used in the United States, and is an environmental contaminant from natural processes in many regions of the United States. Perchlorate has been detected in the drinking water of communities around the United States (9), including Massachusetts (10). It has also been detected in foods such as lettuce and wheat (11, 12). Perchlorate exposure appears to be ubiquitous in the U.S. population (13). A recent study measured perchlorate in the breast milk of 36 women from 18 states and found detectable levels in all of the samples (range, 0.6–2.2 μg/liter) (14). Breast milk iodide and perchlorate concentrations were inversely correlated in the six samples with perchlorate concentrations of at least 10 μg/liter, although there were no correlations between breast milk iodide and perchlorate in the full data set (14).

Another recent study concluded that cigarette smoking decreases breast milk iodine concentrations (15). Cigarette

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Abbreviations: NHANES, National Health and Nutrition Examination Survey; NIS, sodium/iodide symporter.

smoke contains significant levels of cyanide that is metabolized to thiocyanate, a known competitive inhibitor of the NIS. Elevated serum thiocyanate levels may inhibit NIS-mediated transport of iodide in the lactating breast, leading to reduced breast milk iodine levels.

The objective of the present study was to determine whether breast milk iodine concentrations in Boston-area women are adequate for infant nutrition and whether breast milk iodine concentrations may be associated with environmental perchlorate or cigarette smoke exposure. Levels of iodine and perchlorate in breast milk were compared with those measured in 17 brands of infant formulae.

Subjects and Methods

We obtained breast milk and urine samples from 57 healthy Boston-area volunteers (range, 19–45 yr; mean age, 30 ± 6 yr), at 10–250 (median, 48) days postpartum, between July 2002 and April 2006. The local Institutional Review Board approved the protocol, and informed consent was obtained from all participants. Volunteers were recruited through various means, including a community-based new mothers' group, routine postpartum visits at a hospital-based inner-city obstetric clinic, and flyers posted in a hospital lobby. Of the women studied, 72% reported taking prenatal multivitamins, but only three were using iodine-containing multivitamin preparations.

Twenty-seven women completed a questionnaire regarding their demographics and intake of dietary iodine and iodine-containing multivitamins. Spot urinary iodine measurements were obtained from all subjects. Urine perchlorate, creatinine, and cotinine (a metabolite of nicotine in cigarette smoke) concentrations were also measured. Samples of breast milk (approximately 10 ml) were collected at the start of a feed using either hand expression or a breast pump in 27 of the women. Samples of breast milk were collected in 5-ml increments sequentially using a breast pump in the other 30 women. In this subset of 30 subjects, we measured breast milk iodine concentrations both at the start of a feed and sequentially throughout a single feed to assess any potential intrafeed variation. In the women whose breast milk was collected in sequential increments, the mean breast milk iodine concentration is reported. Enough breast milk was available in 49 (86%) and enough urine was available in 56 (98%) of the samples for the measurement of perchlorate. Enough urine was available in 56 (98%) of the samples for the measurement of cotinine. All breast milk and urine samples were obtained within the same hour.

Seventeen brands of infant formulae were also assessed for iodine and perchlorate levels. A single sample of each different type of liquid formula available at a local supermarket was purchased for testing. Nine brands were sold in concentrated form and designed to be diluted by half before use. Iodine and perchlorate levels were measured directly in these samples, and the results were divided by half to reflect the concentration intended for infant use. The other eight brands were sold ready for use.

Breast milk, infant formulae, and urine iodine concentrations were measured spectrophotometrically by a modification of the method of Benotti *et al.* (16). Iodine concentrations were measured at least twice; in 95% of the samples, the initial two measurements were within 15% of each other, and the two values were averaged. In the case where the initial two measurements were not within 15% of each other, a third measurement was obtained, and the average of all measurements was reported. Cotinine measurements were performed by immunoassay (Immulite 2000 Nicotine Metabolite Assay; Diagnostic Products Corp., Los Angeles, CA). Urine creatinine measurements were performed using Jaffe's alkaline picrate method. The perchlorate content of breast milk, infant formulae, and urine samples was measured at the Centers for Disease Control and Prevention laboratories in Atlanta, GA, using ion chromatography-mass spectrometry (17).

All statistical analyses were carried out using SAS version 9.1 (SAS Institute, Cary, NC). Spearman's rank correlation coefficient was used to determine whether linear associations were present, and multivariate linear regression was used to determine significant predictors of breast milk iodine concentration. Intrafeed variation in the iodine content of the subjects whose breast milk was measured sequentially was assessed using repeated-measures ANOVA. Differences in breast milk and urine iodine values between smokers and nonsmokers and differences in measured and labeled infant formula iodine content were assessed using an independent *t* test. Differences in mean values across subject groups were assessed by ANOVA. Differences in median iodine and perchlorate values in breast milk compared with infant formula were assessed using the Wilcoxon rank sum test.

Results

Median iodine content in the 57 breast milk samples was 155 μg/liter [range, 2.7–1968 μg/liter; mean (± SD), 205 ± 271 μg/liter]. There was no significant intrafeed variation in the iodine content of the subjects whose breast milk was assessed sequentially during a single feed. Breast milk iodine concentrations in the three women who reported using iodine-containing multivitamins were 28, 68, and 187 μg/liter. In a subset of 27 women whose use of iodized table salt was determined, there was no significant difference in breast milk iodine levels between the subjects who reported regular, occasional, or no use of iodized salt ($P = 0.16$). There was a slight but significant positive correlation between breast milk iodine content and maternal age ($r^2 = 0.08$; $P = 0.04$) but not infant age ($P = 0.4$). Median urine iodine content was 114 μg/liter (range, 25–920 μg/liter; mean, 155 ± 142).

Perchlorate was detectable in all 49 breast milk samples (median, 9.1 μg/liter; range, 1.3–411; mean, 33 ± 77) and 56 urine samples tested (median, 3.0 μg/liter; range, 0.37–127; mean, 8.2 ± 19). Cotinine was detected in the urine of 32 (57%) of 56 urine samples tested (range, 1.5–1575 ng/ml), with six (19%) of these likely to be smokers (urinary cotinine >500 ng/ml). Mean breast milk iodine was 62 ± 35 μg/liter in the smokers and 221 ± 285 μg/liter in the nonsmokers ($P = 0.0005$), whereas urinary iodine did not differ between these groups ($P = 1.0$). There were significant differences in the mean breast milk perchlorate concentrations between the women recruited from the mothers seen at routine postpartum visits at a hospital-based inner-city obstetric clinic (n = 10; 88.0 ± 150.0 μg/liter), those from the community-based new mothers' group (n = 9; 50.0 ± 62.5 μg/liter), and those recruited by the hospital postings (n = 30; 10.3 ± 13.8 μg/liter) (*P* for difference across the three groups was 0.01). There were no significant differences between breast milk iodine, urinary iodine, urinary perchlorate, and urinary cotinine across these subject groups.

Breast milk and urine iodine content in micrograms per liter were not significantly correlated ($r^2 = 0.06$; $P = 0.08$). A significant positive correlation between breast milk iodine and urine iodine content per gram creatinine was observed ($r^2 = 0.27$; $P < 0.0001$). There was a significant positive correlation between breast milk perchlorate and urine perchlorate concentrations ($r^2 = 0.11$; $P = 0.02$). There were no significant correlations between breast milk iodine and perchlorate concentrations (n = 49; $r^2 = 0.05$; $P = 0.1$) (Fig. 1), including the 23 women whose breast milk perchlorate values were 10 μg/liter or higher ($r^2 = 0.002$; $P = 0.8$). Breast milk iodine and urine perchlorate concentrations ($r^2 = 0.004$; $P = 0.7$) were not significantly correlated. There was a slight but significant inverse correlation between breast milk iodine and urine cotinine concentrations ($r^2 = 0.13$; $P = 0.006$) (Fig. 2). In multivariate models, breast milk perchlorate ($P = 0.9$), urine perchlorate ($P = 0.4$), urine cotinine ($P = 0.2$), and baby

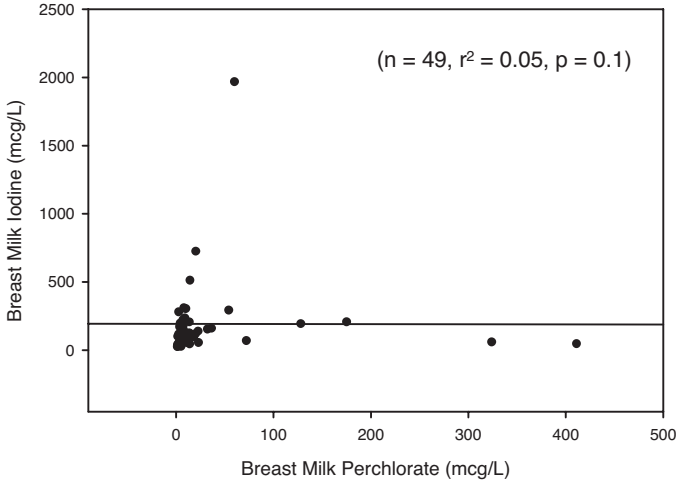

FIG. 1. Correlation between breast milk iodine and perchlorate concentrations.

age ($P = 0.6$) did not predict breast milk iodine levels. Assuming an average daily infant intake of 0.78 liters breast milk (1) and that these breast milk samples are representative, 27 of the 57 samples (47%) did not contain sufficient iodine to meet infants' adequate intake of 110–130 μg/d, as recommended by the Institute of Medicine (Fig. 3).

In the 17 brands of infant formulae, the median measured iodine concentration was 145 μg/liter (range, 84–224 μg/liter), and the median perchlorate concentration was 1.50 μg/liter (range, 0.22–4.1 μg/liter) (Table 1). Measured infant formula iodine concentrations were significantly higher than labeled amounts ($P < 0.0001$). There was no significant difference between the median breast milk and infant formula iodine concentrations ($P = 1.0$), whereas the median breast milk perchlorate concentration was significantly higher than the median infant formula perchlorate concentration ($P < 0.0001$).

Discussion

Iodine is avidly concentrated in the lactating breast, due to increased expression of NIS during lactation (18). Breast milk

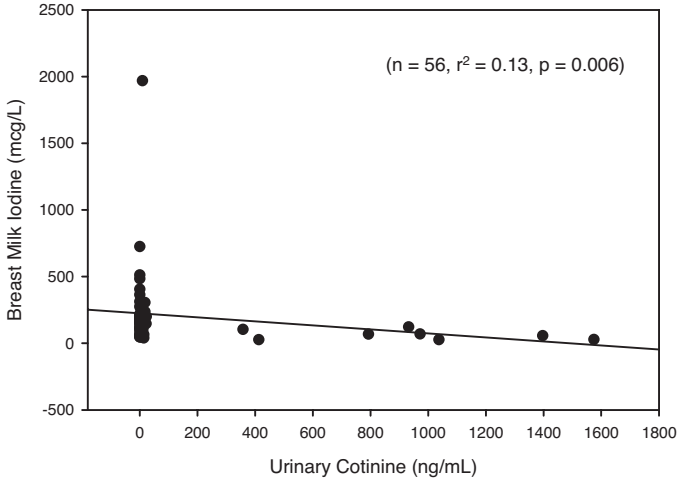

FIG. 2. Correlation between breast milk iodine and urine cotinine concentrations.

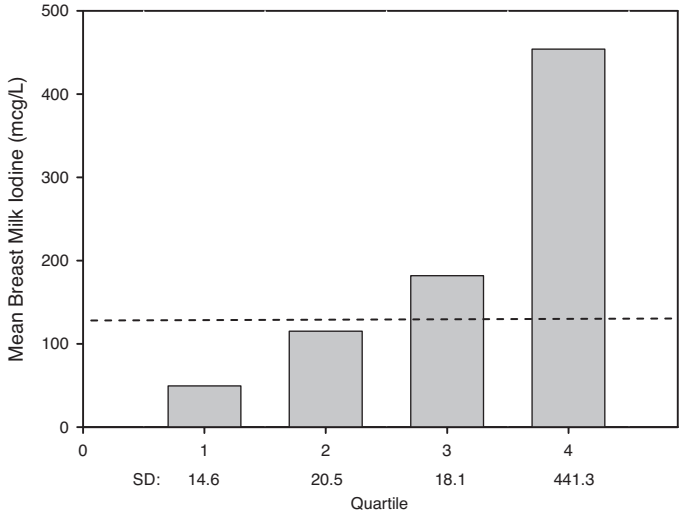

FIG. 3. Mean breast milk iodine content by quartile, with SD shown numerically. *Dotted line* corresponds to approximate breast milk iodine content required to achieve adequate intake (110–130 μg/liter) for an infant age 0–6 months.

iodine levels are highest in transitional milk (2–5 d postpartum) and decrease to stable levels by 10 d postpartum (18). We report that among the 30 subjects whose breast milk was sampled sequentially, there were no significant intrafeed variations in iodine concentration. A recent study suggests, however, that there is a substantial amount of day-to-day and diurnal variation in breast milk iodine excretion (19).

The median breast milk iodide level in a 1984 sample of 37 U.S. women was 178 μg/liter (20), which is similar to the median iodine value of 155 μg/liter observed in our study. However, the median breast milk iodine value in our study was far higher than the median values of breast milk iodide (33.5 and 55.2 μg/liter) observed recently by Kirk *et al.* (14, 19) in two samples of U.S. women. Some, but not all, of this difference may be due to our method of measuring total iodine in contrast to Kirk *et al.* (14, 19), who measured only ionic iodine (iodide); however, approximately 80–90% of iodine in human milk is in the form of iodide (S. Pino, unpublished data). The median breast milk iodine concentration observed in our study was also far higher than the mean value of 38.5 μg/liter reported in 55 Chilean women (21); the iodine content of breast milk from the Chilean women was measured by the same method as reported in the current manuscript (16). Tellez *et al.* (21) in the Chilean study and Chan *et al.* (22) in an Australian study reported that breast milk iodine levels correlate with urinary iodine per gram creatinine but not with unadjusted urinary iodine values, as seen in the present study.

Assuming breast milk intake of 0.78 liter/d (6) as the only source of breastfed infant iodine nutrition, and that single samples are representative of daily breast milk iodine content, which may not be correct due to the day-to-day and diurnal variation in breast milk iodine content noted by Kirk *et al.* (19), 47% of women sampled may have been providing breast milk with insufficient iodine to meet infants' daily requirements. The difference between median breast milk and measured infant formula iodine levels was not signifi-

TABLE 1. Iodine and perchlorate concentrations in 17 brands of infant formulae

Liquid infant formula brand	Labeled iodine (μg/liter)	Measured iodine (μg/liter)	Measured perchlorate (μg/liter)
Milk-based			
Enfamil A.R. Lipil (thickened with rice starch, iron-fortified)	67	224	4.1
Enfamil LactoFree Lipil (lactose-free, iron-fortified)[a]	100	120	0.4
Enfamil Lipil Low Iron	67	158	2.1
Enfamil Lipil with Iron (infant formula)[a]	67	102	1.7
Enfamil with Iron (milk-based)[a]	67	162	2.0
Nestle Good Start with Iron (Supreme, with easy to digest Comfort Proteins)[a]	80	145	0.3
Nestle Good Start with Iron (Supreme, with easy to digest Comfort Proteins)	80	178	0.2
Nutramigen Lipil (lactose-free, hypoallergenic, iron-fortified)	100	193	1.5
Similac Advanced Infant Formula with Iron[a]	40	122	1.5
Similac Alimentum Advance with Iron (protein hydrolysate formula with iron, hypoallergenic)	100	158	2.0
Similac Infant Formula Low Iron	40	153	2.1
Similac Infant Formula with Iron[a]	40	142	1.6
Similac Lactose Free Infant Formula with Iron	60	143	1.4
Similac Neosure Advance with Iron	100	178	2.5
Soy-based			
Enfamil Prosobee Lipil (milk-free, lactose-free, iron-fortified)[a]	100	112	0.3
Enfamil Prosobee Soy Infant Formula (milk-free, lactose-free, iron-fortified)[a]	100	122	0.6
Similac Isomil Soy Formula with Iron (milk-free, lactose-free)[a]	100	84	0.4

All of the iodine and perchlorate levels reported here reflect the concentration intended for infant use.
[a] The nine brands of infant formula that were sold in concentrated form and designed to be diluted by half before use.

cant ($P = 1.0$); however, there was a significant difference between the labeled and measured mean infant formula iodine concentrations ($P < 0.0001$). Assuming an average infant formula intake of 0.86 liter/d (for infants 2 months of age) (23), the labeled iodine concentrations in all 17 (100%) infant formula brands were insufficient to meet the Institute of Medicine's recommended adequate intake of 110 μg/d, whereas 35% of the measured infant formula iodine concentrations contained insufficient iodine levels. Although clinically apparent iodine deficiency disorders are vanishingly rare in U.S. infants, it is possible that breast-fed infants whose mothers' milk is iodine deficient, as well as some formula-fed infants, might experience subtle neurodevelopmental abnormalities. An upper limit for iodine tolerability has not been established in infants.

The question of whether low-level environmental perchlorate exposure has clinical consequences has been extremely controversial (24) and has been the topic of a recent National Academy of Sciences review (7). Median urine perchlorate was 3.6 μg/liter in 2820 spot urine specimens in the most recent NHANES survey (2001–2002) (13), and there was a small positive correlation with serum TSH and a small inverse correlation with serum T_4 values among women, but not men, with urinary iodine values less than 100 μg/liter (25). The developing fetus and infant are likely to be most vulnerable to the adverse effects of perchlorate on thyroid function because they have the highest rate of thyroidal iodine turnover and they require adequate thyroid hormone for normal neurodevelopment. In this study, we found measurable perchlorate levels in 100% of 49 human milk samples tested, with a median value of 9.1 μg/liter. This is higher than the levels reported by Kirk *et al.* (14, 19) in two recent studies (medians, 3.3 and 4.0 μg/liter) and in the infant formulae currently measured (median, 1.50 μg/liter). There was a significant difference in the perchlorate levels among the subjects when grouped by method of recruitment, which may be attributable to the relatively small sample size as well as the demographic differences of the study population. In data from NHANES 2001–2002, non-Hispanic Blacks had lower levels of urinary perchlorate than non-Hispanic Whites (13). Perchlorate was also detectable in all 56 human urine samples tested, with median levels (2.90 μg/liter, and 2.94 μg/g creatinine) consistent with previously published data (17). The source of this perchlorate exposure is unknown and merits further investigation.

Kirk *et al.* (14) previously speculated that milk perchlorate of 10 μg/liter or higher may lead to reduced milk iodide levels. Despite the fact that 47% of our samples contained perchlorate at concentrations of at least 10 μg/liter, we found no correlations between milk perchlorate and milk iodine content. Our results are consistent with the results of Lengemann (26), who found dairy cattle milk iodine excretion unaffected by perchlorate doses less than 0.1 mg/kg·d. A recent study of pregnant and lactating Chilean women consuming tap water known to contain naturally occurring perchlorate (~110 μg/liter) also found no correlation between perchlorate exposure and breast milk iodine or newborn thyroid function tests (21). One possible reason for the lack of correlation in these studies might be the diurnal and day-to-day variation in breast milk concentrations of both iodine and perchlorate (19).

Thiocyanate, as a metabolite of cigarette smoking, is also a known inhibitor of the NIS. Laurberg *et al.* (15) reported that although both smokers and nonsmokers had stable levels of urinary iodine postpartum, smokers (defined as those with urinary cotinine >500 ng/ml) had lower concentrations of breast milk iodine, and their infants had lower concentrations of urinary iodine. Similarly, we found a small but

significant inverse correlation between breast milk iodine and urine cotinine concentrations and found that smokers had significantly lower breast milk iodine levels than nonsmokers. Breastfeeding women should clearly be counseled against smoking for this and many other reasons.

We believe that a larger study of breast milk iodine content and its relationship to perchlorate exposure and maternal iodine nutrition is warranted in U.S. women. Although in the present study we found no correlation between breast milk iodine and perchlorate concentrations, the relatively low levels of iodine and relatively high levels of perchlorate in human milk do raise concerns. One limitation of the study was that we do not know the impact of breast milk perchlorate on the thyroidal iodine uptake and thyroid function of the breastfed infants. The American Thyroid Association has recently identified as a research priority the measurement of breast milk iodine levels in U.S. women and correlation with maternal iodine nutrition and factors such as smoking (27). Very few women in the present study reported routine use of an iodine-containing multivitamin. We feel that there should be more public awareness of the importance of dietary iodine in lactation and that iodine (at least 150 μg) should be included in standard prenatal multivitamins consistent with the recent recommendations of the National Academy of Sciences (7) and the American Thyroid Association (8). It is important to note that epidemiological studies consistently point to the value of human milk as the healthiest food for infants. Thus, the benefits of human milk outweigh possible effects of environmental toxicants present.

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Address all correspondence and requests for reprints to: Elizabeth N. Pearce, M.D., M.Sc., Boston Medical Center, 88 East Newton Street, Evans 201, Boston, Massachusetts 02118. E-mail: elizabeth.pearce@bmc.org.

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