Comparison of neonatal thyroid-stimulating hormone levels and indicators of iodine deficiency in school children

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Abstract

Objectives: To compare thyroid-stimulating hormone (TSH) levels in neonatal cord blood between study sites in Bangladesh, Guatemala and the United States. Also, to compare neonatal TSH results with indicators of iodine deficiency in school children.

Design: Consecutive births and, in school children, cross-sectional surveys.

Setting: Savar, Bangladesh; San Pedro Sacatepequez, Guatemala; and Atlanta, United States.

Subjects: In each study site, cord blood was spotted on to filter paper and TSH levels determined using a sensitive monoclonal assay. In the USA, heel stick blood specimens from newborns spotted on to filter paper were also obtained as well as exposure to iodine-containing antiseptics during the birthing process. Urine specimens were collected from mothers of newborns and tested for iodine concentration. School children in the same areas were surveyed for thyroid size by palpation and ultrasonography, and urine specimens collected for iodine concentration.

Results: Between 141 and 243 cord blood specimens were collected from each study site. The prevalence of elevated cord blood TSH levels ($>5\,\mathrm{mUl^{-1}}$) was high in all study sites, from 58% to 84%. All sites would be categorised as having 'severe' iodine deficiency based on WHO/UNICEF/ICCIDD criteria. Iodine-containing antiseptics were used during 98% of the births in the USA but not in Bangladesh or Guatemala. The neonatal TSH classification indicated more severe iodine deficiency levels than classifications based on urinary iodine and goitre in school children.

Conclusions: In the USA, elevated TSH levels may be partially attributed to use of beta-iodine-containing antiseptics prior to birth. We recommend the cautious interpretation of TSH results in newborns for the assessment of iodine deficiency disorders when iodine-containing antiseptics are used during the birthing process.

Iodine deficiency is a global public health problem and iodine deficiency disorders (IDD) represent the main cause of preventable mental retardation with over a billion people at risk world-wide[1]. Iodine deficiency may result in permanent brain damage in the foetus and infant, and retarded psychomotor development in the child[2]. Other detrimental effects of iodine deficiency include increased incidence of still births, abortions and congenital abnormalities including endemic cretinism. Neonates born in iodine-deficient areas are the most vulnerable to impaired mental development[1,3].

Thyroid-stimulating hormone (TSH) testing in newborns has been used as an indicator for assessing the prevalence of IDD[1,4−12]. Studies in iodine-replete populations in Canada and Australia found the prevalence of elevated TSH levels ($>5\,\mathrm{mUl^{-1}}$, using a sensitive monoclonal antibody test) in *heel* blood filter paper specimens collected three or more days after birth to be between 3% and 5%[1,7]. The distribution of TSH in *cord* blood specimens collected at birth in an iodine-replete population using a more sensitive monoclonal TSH test was not found in the literature.

In November 1992, a group of experts in iodine deficiencies developed an IDD prevalence classification scheme based on the best information available at the time by consensus for various indicators, including neonatal TSH[1]. The present study was conducted to compare several indicators of IDD in an iodine-replete area (the

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USA) and in Bangladesh and Guatemala, countries that had, based on information at the time of the study, mild to severe levels of IDD.

In Bangladesh, national surveys had estimated the prevalence of goitre in school children to be 50% and the proportion of households consuming iodised salt, 44%[13]. The present study was carried out in Savar, located 50 km north-west of Dhaka. In Guatemala, which historically had reported mild to moderate levels of IDD (WHO, 1993), national surveys estimated the prevalence of goitre in school children to be 20% and that iodised salt was consumed in 64% of households[13]. The present study was carried out in eight rural hamlets and in the urbanised municipal seat of San Pedro Sacatepequez, a township located 17 km from Guatemala City. This is a poor, largely agricultural area in which the majority of the population is of indigenous ethnicity from the Kakchiquel post-Mayan linguistic group. In the USA, IDD was a significant problem in the early 1900s, but the US has been considered iodine-sufficient for decades. The study was carried out in the Atlanta metropolitan area.

Since this study focuses on the use of TSH in newborns as an indicator of IDD, it is important to note that many factors may affect TSH in individuals, including: (1) biological variability; (2) a surge in TSH during the first few days of life, attributed to neonatal stress brought on by the birthing process[7,14−16], thus the timing of specimen collection is important; (3) maternal iodine deficiency, which results in slightly elevated TSH levels in the newborn[1,4−8,10,11,17−21]; (4) congenital hypothyroidism, which results in extremely high TSH values in affected infants; (5) more stressful births, which tend to have higher cord TSH levels[10,22−24]; (6) maternal exposure to iodine-containing antiseptics[25−30] and to iodine-containing X-ray contrast media[27], resulting in increased neonatal TSH levels that may last one month or longer[29,30] and also in higher iodine levels in breast milk that also increase neonatal TSH levels[25]; (7) neonatal exposure to iodine-containing antiseptics increases neonatal TSH levels[31,32]; and (8) certain anti-thyroid medications[33], placental transfer of TSH-receptor blocking antibodies[33] and some rare endocrinology conditions can also affect neonatal TSH levels.

In addition to factors that affect TSH levels in individuals, comparison of TSH levels between populations can be affected by: (1) the type of TSH test (monoclonal vs. polyclonal), with polyclonal tests cross-reacting with a number of other factors[10]; (2) the type and grade of blood collection paper; (3) the units in which the results are provided (serum vs. whole-blood units); and (4) the manufacturer of the test kit[34].

In this paper, we examine the use of TSH as an indicator of IDD in newborns and compare this with indicators of IDD in school children (urinary iodine, prevalence of goitre, and prevalence of large thyroid volumes based on ultrasonography). Additionally, the relationship between cord blood TSH and heel blood TSH and predictors of high TSH levels was examined in neonates from the USA.

Methods

For the three study sites, the goal was to collect cord blood spots and maternal urine specimens from consecutive births with the goal of having 200 specimens each. In addition, 400 school children in the same area were to be surveyed during the study period to collect information concerning indicators of IDD. The collection of the information should be considered as convenience sampling rather than representative population-based surveys.

Bangladesh
Cord blood samples were collected by physicians in the local hospital, the study period being between May and November 1996. Maternal urine specimens were collected prior to birth but in some instances collected one day after delivery. A total of 400 children, 7 to 10 years of age, from three schools in the Savar area were surveyed in May 1996. The study was approved by the Administrative Authority of Dhaka University and written consent was obtained from the parents of school children and from the mothers of neonates.

Guatemala
Most of the births were attended by traditional midwives, who made the blood spots on filter paper by pipetting cord blood collected in a glass test tube provided for the study. Maternal urine samples were collected within 15 to 45 days after birth, either by the midwife or a field physician. Cord bloods were collected from births occurring between June 1995 and June 1996. A total of 518 children, 6−16 years of age, from seven schools in the study area were surveyed. The study protocol was approved by the Human Studies Committee of the Center for Studies of Sensory Impairment, Aging and Metabolism (CeSSIAM).

United States
Cord blood samples were collected from October 1996 to January 1997, from newborns born vaginally at Crawford Long Hospital in Atlanta, Georgia. Urine samples were collected from mothers upon admission to the delivery ward during April to July 1996 and October 1996 to January 1997. This hospital serves low- to middle-income groups. Information on newborns was obtained from birth certificates and beta iodine exposure in mothers during hospitalisation prior to birth from medical records. In the State of Georgia, screening of newborns for a number of medical conditions is required by law. Heel stick blood specimens were collected on to filter paper cards (grade 903; Schleicher & Schuell, Keene, NH, USA) and mailed to the State Laboratory. When available, heel stick specimens

with a date of collection were obtained for newborns from whom cord blood samples had been collected. School children were enrolled in the study based on a convenience sample of seven schools in Atlanta metropolitan area (Decatur City Schools and one private school), grades three to five, in March and April 1996. Thyroid volumes by ultrasonography, palpation of the thyroid, weight, height, filter paper blood specimens and urine samples were collected. A total of 305 school children were studied. The Emory University Human Investigation Committee approved the hospital- and school-based studies with written consent obtained from parents or guardians.

Anthropometry

Standing heights and weights were collected in all sites except Guatemala. Height-for-age (HAZ) and weight-for-age (WAZ) Z-scores were calculated using the World Health Organization (WHO)/Centers for Disease Control and Prevention (CDC) growth reference using Epi Info software[35]. Body surface area (BSA) was calculated using the following formula: BSA = weight $(kg)^{0.425}$ × height $(cm)^{0.725}$ × 0.007184. BSA was not calculated for children where the HAZ or WAZ was considered biologically implausible (HAZ or WAZ less than minus six standard deviations ($-6SD$) or greater than $+6SD$).

Thyroid volume

Thyroid volumes were determined using a Philips portable ultrasound unit (model number SDR1200; Philips Ultrasound, Inc., Santa Ana, CA, USA) with a standard 5 MHz transducer (model number LA5056; Philips). Palpation and ultrasonography were performed by one of two physicians in each of the study sites after ensuring standard techniques. Longitudinal and transverse scans were performed to measure the depth (d), width (w) and length (l) of each lobe in millimetres. The volume for each lobe was calculated by multiplying $d \times w \times l \times 0.000479$ and the total thyroid volume calculated by summing each lobe volume. The volume of the isthmus was not included. Abnormal thyroid volumes were calculated using the sex-specific, WHO thyroid-volume-per-body-surface-area reference based on European children[36]. Thyroid volumes greater than the 97th percentile were considered as abnormally large and those less than or equal to the 97th percentile as normal.

Laboratory methods

At all sites, dried cord blood samples were obtained by drops of cord blood spotted on to labelled specimen filter paper cards (grade 903; Schleicher & Schuell) and allowed to dry in air horizontally for several hours. A commercially available neonatal blood spot method (Enzaplate N-TSH; Ciba-Corning, Japan) was used to measure TSH and all specimens were analysed at the Program Against Micronutrient Malnutrition (PAMM) laboratory in Atlanta.

This microplate enzyme-linked immunoassay (ELISA) is based on commonly used TSH-specific antibody sandwich principles and was used because of its high sensitivity (about 2 mU l^{-1}) and assay specificity, which allows clear discrimination at low TSH levels. This has been shown to be an important factor in the utilisation of blood spot TSH as a public health tool for monitoring the severity of iodine deficiency in populations[11]. Internal quality control (QC) results at the PAMM laboratory included four control specimens of different concentrations run in all assays and external quality control through participation in a programme co-ordinated by CDC.

Urine samples were tested for iodine levels using a manual acid digestion method. The samples were treated according to the method of Dunn et al.[37,38], being digested with chloric acid (750 μl, 28% v/v) at 110°C for 50 min. The iodine content was estimated in the Sandell–Kolthoff reaction, in which iodine acts as a catalyst for the reduction of cerium(IV) to cerium(III) by arsenic(III). Unknown urine samples were compared with a set of standards ranging from 0 to $0.95 \mu \text{mol l}^{-1}$ ($0-120 \mu \text{g l}^{-1}$). With the exception of Bangladesh, all urine iodine analyses were performed by the PAMM laboratory. Standard laboratory quality control measures were used during testing to ensure the accuracy of the results, with quality control carried out using PAMM control materials. The PAMM laboratory co-ordinated and participated in an external urinary iodine quality control programme with 25 laboratories around the world and the laboratory methods used by the PAMM laboratory had been found to be comparable with other methods[38]. Urinary iodine analyses from Bangladesh were performed by the Ministry of Health using the same methods and quality control. A sub-sample of 100 urine specimens tested by both PAMM and Bangladesh had a high correlation (Spearman rank correlation = 0.91, $P < 0.001$); Bangladesh results tended to be higher than PAMM results (median of $60.3 \mu \text{g l}^{-1}$ and $50.0 \mu \text{g l}^{-1}$, respectively; Wilcoxon signed rank test $P < 0.001$); and there was no statistically significant difference in classifying children as low urinary iodine ($<100 \mu \text{g l}^{-1}$ vs. $\geq 100 \mu \text{g l}^{-1}$; exact sign test $P = 0.13$).

Statistical methods

Epidemiological criteria have been established by WHO, the United Nations Children's Fund (UNICEF) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) (1994) to classify populations in terms of the severity of IDD. For neonates, the proportion with a TSH level $>5 \text{ mU l}^{-1}$ whole blood is classified as follows: mild, $3-19.9\%$; moderate, $20-39.9\%$; severe, $\geq 40\%$. For median urinary iodine levels ($\mu \text{g l}^{-1}$) in school-aged children, the classification is: mild, $50-99 \mu \text{g l}^{-1}$; moderate, $20-49 \mu \text{g l}^{-1}$; severe, $<20 \mu \text{g l}^{-1}$. Based on the prevalence of goitre and for thyroid volume >97th percentile in school children: mild, $5-19.9\%$; moderate, $20-29.9\%$; severe, $\geq 30\%$.

The Epi Info software program[35] was used for data entry and analysis. TSH distribution was analysed by two methods: one based on the median value because TSH is not normally distributed, and the other by presenting the prevalence of elevated TSH ($>5\,\mathrm{mUl}^{-1}$). The Chi-square test was used to assess the prevalence of elevated TSH between populations and the Wilcoxon rank sum procedure to compare TSH distributions between groups. The Wilcoxon signed rank test was used for the matched cord and heel TSH values. Exact mid-*P* confidence intervals were calculated using the PEPI software program[39]. Confidence intervals for the median were determined using methods described by Gardner and Altman[40].

Results

The proportion of cord bloods with elevated TSH levels ranged between 58% in Guatemala and 84% in Bangladesh (Table 1). On the basis of WHO criteria, all areas would be classified as having severe IDD. Maternal median urinary iodine levels ranged from $96\,\mu\mathrm{g\,l}^{-1}$ in Bangladesh to $120\,\mu\mathrm{g\,l}^{-1}$ in Guatemala. If the WHO urinary iodine criteria for school children were applied to the mothers, Bangladesh would be classified as having mild IDD and Guatemala and the USA as having no IDD.

School children ranged from 7 to 10 years of age in Bangladesh (mean = 8.8 years, 95% confidence interval (CI): 8.7, 8.9), from 6 to 16 years in Guatemala (mean = 9.8 years, 95% CI: 9.7, 10.1) and from 6 to 12 years in the USA (mean = 9.2 years, 95% CI: 9.1, 9.4). There were approximately equal proportions of males and females in each site. School children in Bangladesh had a mean height-for-age Z-score of -1.7 (95% CI: -1.8, -1.6) and mean weight-for-age Z-score of -2.0 (95% CI: -2.1, -1.9); the corresponding figures for the USA were 0.4 (95% CI: 0.3, 0.5) and 0.8 (95% CI: 0.6, 0.9), respectively. The prevalence of goitre ranged from a low of 2% in the USA to 27% in Bangladesh. The prevalence of large

thyroids using ultrasonography (based on WHO thyroid-volume-for-BSA reference) was 0% in the USA and 26% in Bangladesh. For the European thyroid-volume-per-BSA reference, the lowest value of BSA was 0.8; 12% of the children in Bangladesh were below this BSA value and therefore excluded from the calculation. Thyroid volume per BSA could not be calculated for the Guatemala data because weights and heights were not collected. Median urinary iodine levels in school children classified Bangladesh as having mild IDD and Guatemala and the USA as having no IDD.

More detailed information was collected from the births in the USA. The median age of the mothers was 26 years, 83% were African-American, 43% married, and 58% had completed one to three years of college. Forty-four per cent of the newborns were female and 12% weighed $<2500\,\mathrm{g}$. Of 459 births that occurred during the study period, 243 (53%) cord blood samples were obtained. Of these, 82.3% had a TSH level greater than $5\,\mathrm{mUl}^{-1}$ with a median of $8.3\,\mathrm{mUl}^{-1}$ (Table 2). Cord samples were matched with birth certificates in 177 cases (73%). Of the newborns from whom a cord sample was collected, we were able to match 127 (52%) with heel samples. There were no significant differences between the 127 infants with heel samples and the 50 infants without heel samples in terms of mother's age, parity, marital status, or other demographic information available from birth certificates. Ninety (71%) of these heel samples indicated the date the sample had been collected.

As can be seen in Table 2, cord blood had high levels of TSH, day one heel stick specimens had slightly higher levels, and then lower TSH levels thereafter. For 173 (71%) mothers from whom cord blood specimens were collected, information and timing of beta iodine exposure were determined from medical records for intravenous (IV) insertion, epidural anaesthesia and bladder catheterisation. The exposure for IV and epidural insertion was skin cleansing with beta iodine, while for catheterisation a more exhaustive cleansing of the perineum. Ninety-eight

Table 1 Comparison of newborn TSH levels, maternal urinary iodine levels, and measures of IDD in school children from study sites in Bangladesh, Guatemala and the United States, 1996−97

Group and indicator		Bangladesh	Guatemala	United States
Neonatal cord blood, TSH $>5\,\mathrm{mUl}^{-1}$	Numerator/denominator	174/208	82/141	200/243
	Percentage (95% CI)	84 (78−88)	58 (50−66)	82 (77−87)
	WHO classification	Severe	Severe	Severe
Mothers, urinary iodine ($\mu\mathrm{g\,l}^{-1}$)	Sample size (*n*)	197	174	231
	Median (95% CI)	96 (81−111)	120 (99−149)	105 (90−117)
School children, goitre	Numerator/denominator	108/399	75/518	7/305
	Percentage (95% CI)	27 (23−32)	15 (12−18)	2 (1−5)
	WHO classification	Moderate	Mild	None
School children, abnormal ultrasound*	Numerator/denominator	90/351	Data not available	0/300
	Percentage (95% CI)	26 (32−31)		0 (0−1)
	WHO classification	Moderate		None
School children, urinary iodine ($\mu\mathrm{g\,l}^{-1}$)	Sample size (*n*)	400	458	284
	Median (95% CI)	73 (66−81)	181 (155−200)	282 (253−308)
	WHO classification	Mild	None	None

* European reference, thyroid volume for body surface area $>$97th percentile.

Table 2 Thyroid-stimulating hormone (TSH) results from newborns, comparison of cord blood and heel stick specimens, Crawford Long Hospital, Atlanta, GA, 1996−97

Specimen	Number of samples	Median TSH (mUI^{-1}) (95% CI)*	% of specimens with TSH > 5 mUI^{-1}, whole blood (95% CI)†
Cord blood	243	8.3 (7.4, 9.4)	82.3 (77.1, 86.7)
Heel blood, day 1	14	8.5 (5.2, 13.1)	85.7 (60.3, 97.5)
Heel blood, day 2	48	7.5 (6.0, 8.6)	79.2 (66.0, 88.9)
Heel blood, day 3+‡	28	4.7 (2.6, 5.4)	42.9 (25.7, 61.4)

* 95% confidence intervals around the median[40].
† 95% exact mid-*P* confidence intervals.
‡ Twenty-four samples were collected on days 3 to 7, and the remainder on days 8 to 34.

per cent of the mothers had at least one of these exposures: 98% received an IV insertion, 62% had an epidural and 34% were catheterised (Table 3). No significant differences in cord TSH levels were found for each exposure (Table 3) and there was a non-significant trend of higher cord TSH levels for procedures performed 12 or more hours prior to birth compared to within 12 hours of birth (Table 3).

Discussion

The relationship between cord blood TSH and heel stick TSH collected three or more days after birth is not clear. Some reports indicate that the TSH levels are approximately the same while others report cord blood values being higher than heel stick results collected three or more days after birth. Differences between reports could be due

to differences in the factors that affect TSH values as listed in the Introduction.

The WHO/UNICEF/ICCIDD neonatal TSH classification[1] categorises Bangladesh and Guatemala as being more severely affected compared with the indicators for school children (goitre, ultrasound and urinary iodine). This could be a result of: (1) iodine deficiency being a more serious problem in pregnant women and the developing foetus, perhaps due to higher iodine requirements and/or different levels of iodine intake/absorption; (2) the foetus may be more sensitive to mild iodine deficiency; and (3) the TSH classification scheme may need adjustment, with the current cut-off values categorising IDD levels more severe than other indicators of IDD.

In the USA, the elevated cord and heel blood TSH may be partially due to maternal exposure to beta-iodine-containing antiseptics prior to birth. However, some of this elevation could be due to inadequate iodine intake in adult US women. Among women in the study, the median

Table 3 Thyroid-stimulating hormone (TSH) results from newborns, comparison of cord blood specimens by type of procedures performed and time between procedure and birth, Crawford Long Hospital, Atlanta, GA, 1996−97

Procedure	Group	*n*	Median TSH (mUI^{-1})	*P*-value
IV	Yes	170	8.5	0.522
	No	3	8.7	
Epidural	Yes	107	9.2	0.245
	No	66	8.2	
Catheterisation	Yes	58	8.2	0.438
	No	115	8.7	
Combinations of procedures	None	3	8.7	0.460
	IV only	58	8.1	
	IV and epidural	54	10.2	
	IV and catheterisation	5	8.2	
	All three	53	8.2	
Time procedure performed prior to birth				
IV	<12 h	125	8.4	0.300
	≥12 h	44	10.2	
Epidural	<12 h	95	9.1	0.300
	≥12 h	12	12.7	
Catheterisation	<12 h	53	8.2	0.150
	≥12 h	2	14.9	

Median times from procedure to birth: IV, 10 h; epidural, 4 h; catheterisation, 3 h. Exact times for initiation of IV was not known for one woman; for catheterisation, time was not known for three women. *P*-values for comparison of two groups based on Wilcoxon rank sum test; for more than two groups, based on Kruskal–Wallis test.

urinary iodine of $105\,\mu g\,l^{-1}$ is borderline mild IDD; however, the interpretation of the urinary iodine levels may be complicated by the fact that the women were about to give birth. Results from NHANES surveys indicate that the median urinary iodine level for women in the US population has declined from $300\,\mu g\,l^{-1}$ in 1971–74 to $130\,\mu g\,l^{-1}$ in 1988–1994[41]. A previous report[38] of casual urine specimens collected among 90 adults in Atlanta had a median urinary iodine level of $84\,\mu g\,l^{-1}$.

Results of the present study may not be representative of the study sites given the consecutive sampling of neonates and the convenience sampling of school children in the same area. However, given that the distribution of iodine deficiency or sufficiency in a limited geographic area is usually homogeneous, the results found in this study probably do not differ systematically from the true prevalence in the study sites. Results from the neonates in the Atlanta area should be interpreted cautiously because of the potential selection bias for which information was available for infants with known TSH heel specimens and iodine-containing antiseptics exposure. However, no significant differences in demographics were found between infants with or without heel specimen results.

In assessing iodine deficiency, we recommend that the TSH criteria proposed by WHO/UNICEF/ICCIDD be used cautiously for populations in which iodine solutions are used during prenatal procedures. Further study is needed to: (1) determine the appropriate cut-off values for defining mild, moderate and severe levels of IDD based on neonatal TSH and the relation between cord and heel stick specimen levels in areas where beta iodine is not used during the birthing process; and (2) determine whether the cut-off value $>5\,mU\,l^{-1}$ is appropriate for monoclonal TSH kits by different manufacturers.

Acknowledgements

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