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Title Page

Short title: Neonatal TSH in Northern Ireland 2003-2014

Title: Neonatal TSH levels in Northern Ireland from 2003 to 2014 as a measure of population iodine status

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Abstract

Objective: The re-emergence of iodine deficiency in the UK has recently been reported in a large cohort of teenage girls including from Northern Ireland (NI) using the gold standard spot urinary iodine concentration. We wished to explore and confirm this by analysing neonatal thyroid stimulating hormone (nTSH) levels in the NI population.

Design We analysed the nTSH heel prick tests results from the NI national screening database between 2003 and 2014. The WHO propose a definition for population iodine sufficiency at <3% of the population with nTSH results >5 mIU/L.

Methods Anonymised results from 288,491 nTSH tests were retrieved and prevalence rates of results at increasing cutoffs including > 2mIU/L and >5mIU/L calculated. We also assessed for possible seasonal variation in nTSH results.

Results An overall population prevalence of 0.49% with TSH >5 mIU/L was found, indicating population iodine sufficiency with no year attaining a prevalence >3%. The prevalence of nTSH >2mIU/L decreased to 4.1% in 2007 and subsequently increased to 9.8% in 2014. Modest seasonal variation was also detected, with higher levels among April/May births.

Conclusions The neonatal TSH database suggests iodine sufficiency in the NI population. However, the rising frequency of results >2mIU/L may indicate an emerging mild iodine deficiency. This is one of the largest and longest studies of its kind in the UK and the first carried out in NI. The summer months may be a time of increased risk for iodine deficiency in our pregnant women whose requirements are increased and who are not currently targeted by any iodine fortification programme in the UK.

259 words

Introduction

Iodine is an essential trace element required for production of thyroid hormones, and an adequate supply of dietary iodine is of particular importance during pregnancy due to the increased demands on the maternal thyroid to compensate for foetal requirements¹. Severe iodine deficiency during development results in cretinism and growth retardation². At the mild end of the spectrum observational studies have shown associations between both mild maternal iodine deficiency and decreased child cognition³. Within the United Kingdom (UK) and Ireland, for many years, iodine intakes were thought to be adequate. More recently, a survey in 2011 reported iodine levels in over 700 teenage girls living across the UK⁴. Results suggested that this group were mildly iodine deficient, with a median urinary iodine concentration (UIC) of 80 µg/L (deficiency <100µg/L). Published data from the Republic of Ireland (ROI) also indicated mild deficiency in the general population in the 1990s and, more recently, in pregnant women^{5,7,8}.

Iodine is found in a range of foods, with the richest sources being fish and dairy products. Within Ireland and the UK, milk and dairy products tend to be the main sources of dietary iodine,^{9,10}. The amount of iodine in foods varies according to the iodine content of the soil, time of year (with iodine content of products such as milk being higher in winter as compared to summer months) and farming techniques (use of iodine containing cattle feed and cleaning agents). The UK and ROI have no formal iodine fortification programme in place, so that iodine status depends entirely on dietary intake. This contrasts with many European countries which have a programme of salt iodization in place⁵.

Population iodine status may be assessed in a number of ways although the gold standard remains population median spot urinary iodine concentration⁶. Other methods include prevalence of goitre, and blood thyroglobulin concentrations. The World Health Organisation (WHO) has further proposed that neonatal thyroid stimulating hormone (TSH) levels may also be used to assess the iodine sufficiency in populations and to investigate the effect of iodination programmes⁵.

Screening programmes for nTSH are predominately to detect and monitor congenital hypothyroidism where nTSH ≥ 20 mIU/L is considered diagnostic and a nTSH ≥ 10 mIU/L warrants repeat sampling. Screening for neonatal hypothyroidism was started in the UK between 1979 and 1981¹¹. Neonatal TSH is considered to be a sensitive marker of iodine status because of the relatively low iodine content of the neonatal thyroid and high turnover. In the presence of iodine deficiency, iodine turnover within the neonatal thyroid is further heightened, resulting in hyper stimulation of TSH¹². The WHO suggests that, within a population, a prevalence of <3% of nTSH values above 5mIU/L may be used to indicate iodine sufficiency⁵. It has also been suggested that, rather than absolute cut-offs, nTSH trends over time may be a more suitable method of monitoring iodine status in mildly deficient populations^{13,14}. Such a trend was identified in a study of nTSH in ROI births between 1995-2006¹³. In this study, according to the WHO cut-off, the Irish mothers were considered iodine sufficient during that time. However a year on year upward trend of TSH >2mIU/L was observed. The authors pointed to the potential for the population to become iodine deficient and advocated continued monitoring of blood spot neonatal TSH levels into the future.

Studies have been undertaken in Belgium, Wales and Australia, with considerable variation observed in neonatal TSH levels ^{13,15,16}. In the majority of these studies, when applying the WHO recommended cutoff, authors concluded that the frequency of TSH concentrations above 5mIU/L was unexpectedly low, considering that within those countries there were numerous reports of mild iodine deficiency, either in the general population or among cohorts of pregnant women. Therefore this cut-off is felt by some to be insensitive when considering iodine levels in mildly deficient populations. This study aimed to explore trends in nTSH levels in the Northern Irish population between 2003 and 2014.

Subjects and Methods

NI TSH neonatal screening

As part of the national neonatal screening programme, all babies born in NI have a bloodspot nTSH measurement taken from a heel prick sample provided on day 5-8 after birth¹¹. For the purpose of this investigation, anonymised access was obtained of nTSH results from samples collected between January 2000 and August 2014.

As this research was limited to the anonymous, secondary use of information, previously collected in the course of normal care, the researchers sought and were granted ethical approval by the NHS Research Ethics committee (reference: 14/SC/1331) and governance approval from the Belfast Health and Social Care Trust (reference: 14113IY-AS).

Within the Northern Ireland Regional Endocrine Laboratory, blood TSH has been measured by dissociation-enhanced fluoroimmunoassay (DELFI) on an autoDELFI analyser since 2000 (Perkin Elmer Life & Analytical Sciences, Bucks, UK: www.perkinelmer.co.uk/lab-solutions). Although data were available from 2000, there was a considerable spike in nTSH levels in 2002. It is thought that this may relate to a change from using wet to dry plates and a change in the paper used with the autoDELFI around this time. It was felt that data collected before this change in methodology might not be comparable and so was excluded.

Statistical Methods

Time series methods were employed to investigate the long-term trends and seasonality in the monthly nTSH results during the period from January 2003 to August 2014. Results were categorised using cut-points of >2, 5, 10 and 20mIU/L for consistency with previous publications^{14,15}. Analysis of the long term trends in the proportions of results exceeding these cut-points was first conducted using the Joinpoint regression program (Version 4.2 – June 2015; Statistical Methodology and Applications Branch and Data Modelling Branch, Surveillance Research Program National Cancer Institute, Bethesda, MD, USA) which was developed for surveillance of trends in incidence rates¹⁷.

Having established the long-term trends, residuals were calculated and submitted to a multiple regression analysis incorporating cosine and sine terms to represent months of the year. The cosine and sine values were assigned in accordance with angles when months were arranged on the circumference of a circle (January=15°, February=45°, ..., December=345°). Robust standard error estimates were used in the multiple regression (Stata release 12, College Station, Texas) to attenuate possible exaggerated significance caused by autocorrelation in the time series. The amplitude of the seasonal component was estimated as $\sqrt{b_{\sin}^2 + b_{\cos}^2}$, and the peak angle as $\tan^{-1}(b_{\sin}/b_{\cos})$ with the quadrant determined by the signs of the regression coefficients, $b_{\sin}$ and $b_{\cos}$ ¹⁸.

Results

After removal of a small number of repeat results, a total of 288,491 TSH results for NI for the 140 month period were received for analysis. Results were categorised using cut-points of >2, 5, 10 and 20mIU/L and aggregated according to month of sampling. The average number of samples per month was 2061 (range 1622-2329).

Between the years of 2003-2014, 6.2% and 0.49% of neonates had blood TSH concentrations >2mIU/L and >5mIU/L, respectively (Table 1). In no year over the collection period did the proportion of TSH concentrations >5mIU/L rise above 3%.

Joinpoint analysis of the monthly results showed no long term trends for TSH >5mIU/L but that the prevalence of TSH >2mIU/L decreased to a minimum of 4.1% for the year 2007 and increased to 9.8% for the year 2014 (Figure 1). This represents an annual percentage increase of 0.6% (95% CI 0.4-0.8) ($p<0.0001$).

The seasonality for results >2mIU/L and >5mIU/L conformed closely to a sinusoidal (sine wave) pattern (Figure 2). The fitted peak was in early-May with the percentage for >5mIU/L varying about the 0.49% average by $\pm 0.09\%$ (i.e. from 0.40% to 0.58%). The >2 mIU/L analysis showed a peak in mid-April with an amplitude of $\pm 0.7\%$ about the 6.2% average.

Results for nTSH frequency >10 and >20mIU/L were 0.13% and 0.06% respectively. There was no evidence of seasonality with either the >10mIU/L or the >20mIU/L cut-points.

Use of robust variance estimates in the multiple regression to mitigate the effects of autocorrelation did not materially alter the findings.

Discussion

Based on the WHO proposal of iodine sufficiency the population of NI are considered iodine sufficient between 2003 and 2014, with a neonatal population prevalence of TSH values $>5\text{mIU/L}$ at $\sim 0.5\%$. The WHO first recommended the cut off of 3% nTSH $>5\text{mIU/L}$ in its 1994 guideline but this was removed from the 2001 guideline amid a lack of consensus regarding the potential impacts of sampling, antiseptic use and collection papers used. It was re-inserted in its 2007 guideline citing the study by Zimmerman et al in which the frequency of nTSH $>5\text{mIU/L}$ (measured at 3-4 days) decreased from 2.9% to 1.7% after the institution of an iodized salt program in Switzerland¹⁹.

It has been suggested that the cut off of 3% frequency of nTSH $>5\text{mIU/L}$ is not sensitive enough to detect mild iodine deficiency. This is because several studies have observed median urinary iodine concentration, which is still regarded as the gold standard, within the mildly deficient range which was not accompanied by a $\geq 3\%$ frequency of nTSH $>5\text{mIU/L}$ among the same populations (Table 2).

Although there is no matched maternal urinary iodine data in NI that corresponds with the years 2003-2014 we can point to three local cohorts with urinary iodine sampling performed around these time frames. Firstly, the NI subset of the UK schoolgirl cohort from 2009 was found to be mildly iodine deficient⁴. We have also reported recently, in abstract form, low median urinary iodine levels in a cohort of NI pregnant women from 2014-2015 which was found throughout all trimesters and into the post-partum period²⁰. However, we have also reported in abstract form a further cohort of schoolgirls surveyed from NI in 2014-2015 as part of a larger survey in the whole of Ireland which was found to be iodine sufficient albeit at the lower end of the normal range²¹. We have found significant difficulties in sampling schoolgirls using the gold standard method of median spot urinary iodine concentration because of reticence about participation among this age group. This means that sampling biases are likely to explain some of the varying results from these studies. Overall we consider these cohorts in NI to fit into a pattern of borderline sufficiency and at times mild iodine deficiency.

A lower cut-off of $>2\text{mIU/L}$ for assessing population iodine status has been suggested by some authors. Our frequency at a cut-off of $>2\text{mIU/L}$ was 6.2% compared to the Welsh cohort of 10.9-11.9% and the Belgian cohort at a frequency of 21-40%^{13,15} (see Table 2). Each of these geographical areas has been previously documented to have mild iodine deficiency.

It has been suggested that trends in blood spot TSH within the normal range should also be examined for changing iodine status among populations. The percentage of TSH values at the lower cut off $>2\text{mIU/L}$ in our study showed an increase from 2007 onwards. An increasing trend $>2\text{mIU/L}$ was also observed in babies born in ROI between 1995-2006¹⁴. The authors suggest that this coincided with reports of a decline in maternal urinary iodine in ROI thus supporting an association. Peters et al reported that the frequency of nTSH $>4\text{mIU/L}$ in London increased from 2006 to 2012 but there is no data in this study for frequency $>2\text{mIU/L}$ ²².

Our frequency of blood spot nTSH $> 5\text{mIU/L}$ (0.49%) is substantially lower than the published ROI cohort (2.4-3.6%) in babies born between 1995-2006, the Welsh cohort (1.5%) between 2011-2013, the Belgian cohort (2.6-3.3%) between 2009-2011 and the Australian cohort (2.2%) in 2004 (Table 2). Potential explanations for these differences include the timing of sampling and also differing TSH

methodologies but the variation could also be due to potential differences in geographical and nutritional factors between the cohorts¹³⁻¹⁶.

The timing of blood sample collection is likely to impact on nTSH results. Lott et al. have described the decline in blood spot TSH in American newborns over the first days of life with the 97.5th centile TSH dropping from 17 mIU/L at 2–3 days to 12 mIU/L at ≥4 days²³. Guidance on when samples are collected differs depending on National Screening Programme Centre standards¹¹. The Belgian cohort had TSH collected three to five days after birth which may, in large part, explain their higher levels while the Welsh cohort collected at five to eight days which was like the NI cohort. The Welsh authors used the same methodology and assay as the current study and they noted a difference between day 4 and day 5 measurements (1.5% vs 0.99% with nTSH >5mU/L). We do not have a breakdown of samples per day in this study. Sampling was encouraged, and usually happened, on or around day 5.

Blood spot sampling quality may impact on nTSH results. Samples in this study were processed from one centre (Regional Endocrine Laboratory, Belfast) which was subject to the UK External Quality Scheme with satisfactory reports across this period. Sample acceptance criteria did not change during this period and so sample quality would not have varied significantly. However, within the Belgian cohort, various methods were employed to measure nTSH levels over a three year period. Some methodological bias may have remained despite the authors' attempts at standardisation resulting in a higher percentage of raised nTSH values.

Geographical variation of iodine content of locally available water, milk, eggs and fish are possible contributing factors to nTSH variations. Further factors surrounding the pregnancy and birth of neonates may also impact on nTSH values, but robust data are not always available for scrutiny. For example birth weight and the use of iodine containing antiseptics have been associated with variations in nTSH values^{13,24,25}.

Ethnicity affecting nTSH is now recognised with higher levels seen in Pakistani, Bangladeshi and Chinese populations. Although we do not have a breakdown of results according to ethnicity the NI census data demonstrates very low levels of ethnic diversity over time (99.3% and 98.3% coded as white in 2001 and 2011 respectively)²².

Our study demonstrated a modest seasonality in nTSH, with levels rising within the normal range during spring/summer months of March to August indicating lower maternal iodine stores as compared to September to February. Seasonality of cases of congenital hypothyroidism have been described in some but not all cohorts²⁵⁻²⁷. Seasonality of nTSH results in the upper end of the normal range rather than seasonality of cases of confirmed congenital hypothyroidism may be a more sensitive marker of iodine deficiency for a population at the lower end of iodine supply. Our results were similar to the ROI and Belgian but not the Welsh cohort¹³⁻¹⁵. Our results mirror the findings among a large cohort of UK schoolgirls demonstrating seasonal variation in median urinary iodine concentration with lowest levels in the summer months⁴. The mechanism of this could in part be due to the previously reported seasonal variations in dairy produce (the principal source of dietary iodine in UK and Irish diets) with lower levels of iodine found in foods in summer months when content of fodder changes¹⁰. The peaks in nTSH in the current study were seen in late spring as opposed to the summer months so this was slightly unexpected. A further mechanism may involve

seasonal vitamin D metabolism affecting the hypothalamic-pituitary-thyroid axis with recent studies indicating an inverse relationship between vitamin D levels and TSH ^{28,29}.

This article is the first publication of its kind from Northern Ireland and one of the largest cohorts in the UK. Results suggest no severe iodine deficiency in this population using over 280,000 nTSH samples. Given the controversy with WHO recommendations we feel the data is useful to the current debate on population monitoring for iodine deficiency. Ongoing surveillance with this method has the advantage of being inexpensive but frequency of values >5mIU/L is not likely to be a good marker of mild iodine deficiency. The value of trends at lower cut off levels of nTSH remains to be seen but shows some promise in identifying populations at risk of mild iodine deficiency. For example significant rises in frequency of nTSH >2mU/L might be considered a trigger to re-evaluate the population with urinary iodine concentrations. Seasonal variation in neonatal TSH has also been demonstrated and may reflect a population at the borderline of iodine sufficiency and therefore vulnerable to seasonal environmental and husbandry shifts. As our population is currently unprotected by any iodine fortification programme these results again raise the need for iodine nutritional guidance for pregnant women in whom iodine requirements are increased.

Declaration of Interest: We declare no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Reference No: 01-2013

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Table 1 Percentage of Northern Ireland neonatal blood TSH values >2mIU/L, >5mIU/L, >10mIU/L and >20mIU/L in 2003-2014

Year	Results N	>2mIU/L		>5mIU/L		>10mIU/L		>20mIU/L	
		n	%	n	%	n	%	n	%
2003	21,935	1,384	6.3%	96	0.44%	26	0.12%	7	0.03%
2004	23,031	1,549	6.7%	136	0.59%	33	0.14%	11	0.05%
2005	23,072	1,356	5.9%	119	0.52%	31	0.13%	17	0.07%
2006	24,477	1,299	5.3%	118	0.48%	23	0.09%	6	0.02%
2007	25,211	1,031	4.1%	92	0.36%	26	0.10%	14	0.06%
2008	26,139	1,257	4.8%	96	0.37%	31	0.12%	14	0.05%
2009	25,759	1,444	5.6%	148	0.57%	52	0.20%	29	0.11%
2010	26,447	1,766	6.7%	136	0.51%	37	0.14%	20	0.08%
2011	26,260	1,761	6.7%	104	0.40%	17	0.06%	8	0.03%
2012	25,756	1,784	6.9%	134	0.52%	38	0.15%	17	0.07%
2013	24,287	1,650	6.8%	121	0.50%	29	0.12%	14	0.06%
2014 #	16,117	1,580	9.8%	107	0.66%	26	0.16%	16	0.10%
Total	288,491	17,861	6.2%	1,407	0.49%	369	0.13%	173	0.06%

To August 2014

Table 2: Comparison of neonatal TSH screening programme studies and contemporaneous population surveys of urinary iodine concentration

Location	Years	No. neonates	Timing (days)	Seasonality	TSH >5mU/L (%)	TSH >2mU/L (%)	Contemporaneous population surveys of UIC in region		
							Year	Cohort	Deficiency reported
Australia ¹⁶	2004	824	2-3	no	2.2	n/a	2004	pregnant women ¹⁶	✓
Rep of Ireland ¹⁴	1995-2006	73,019	5-8	yes	2.4-3.6	19.5-29.3	2004-05	pregnant/ non-pregnant women ⁸	✓
Belgium ¹³	2009-2011	377,713	3-5	yes	2.6-3.3	21.0-40.6	2010-11 2010-11	primary schoolchildren ³⁰ pregnant /non-pregnant women ^{30,31}	x ✓
N Thames England ²²	2006-2012	824,588	5-10	not explored	0.5	n/a	2009	London teenage girls ⁴	✓
Wales ¹⁵	2011-2013	104,992	5-8	no	0.9	10.9-11.9	2009	Cardiff teenage girls ⁴	✓
N Ireland (current)	2003-2014	288,491	5-8	yes	0.5	4.1-9.8	2009 2012-13 2014-15 2014-15	teenage girls ⁴ primary schoolchildren ³² pregnant women ²⁰ teenage girls ²¹	✓ x ✓ x-borderline normal

UIC: Urinary Iodine concentration

n/a – not available

Figure 1

Northern Ireland TSH monthly time series data for percentage >5mIU/L (Figure 1a) and >2mIU/L (Figure 1b) with super-imposed long-term trend by Joinpoint (orange) and fitted seasonal pattern (green)

Figure 1a

Figure 1b

Figure 2

Plot of percentage of children with nTSH >5 mIU/L (Figure 2a) and nTSH >2 mIU/L (Figure 2b) by month in 2003-2014. Error bars show 95% confidence limits. Fitted seasonal trend (dash)

Figure 2a

Figure 2b