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THYROID DYSFUNCTION IN PRETERM NEONATES EXPOSED TO IODINE*

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ABSTRACT

Background Infants <32 weeks' gestation should not be exposed to topical iodine and its avoidance is recommended during pregnancy and breast feeding. Exposure to contrast media and topical iodine are frequently used in many preterm neonates.

Aim To determine whether thyrotropin levels in preterm infants are affected by exposure to intrapartum/neonatal topical iodine and/or use of iodinated contrast media.

Design Infants <32 weeks' gestation were recruited. Maternal and neonatal exposure to iodinated contrast media and topical iodine was recorded; levels of thyrotropin and thyroxine were measured from blood-spot card on postnatal days 7, 14, 28 and the equivalent of 36 weeks' gestation.

Results 125 infants were exposed to topical iodine/contrast media and 48 infants were unexposed. No infants were treated for hypothyroidism; 3 infants (exposed group) had transient hyperthyrotropinaemia. Mean thyrotropin levels were significantly higher on postnatal days 7, 14 and 28 in infants exposed to topical iodine prior to caesarean section compared to unexposed infants; a relationship which persisted after adjustment.

Conclusions In the context of this study neonatal thyroid dysfunction was seen following exposure to iodine via caesarean section but not via exposure to contrast media.

188 words

INTRODUCTION

The iodine requirement for healthy preterm infants is estimated, from balance studies, to be 30-40 μg/kg/day [1,2]. Newborn infants receive iodine through three main sources: parenteral nutrition, enteral nutrition and breast milk. Most preterm infants are on parenteral nutrition initially, and gradually change to enteral nutrition as their clinical condition improves. The current guideline for iodine intake in enteral nutrition for preterm infants is 11-55 μg/kg/day [3]; whereas the current recommended iodine intake in parenteral nutrition regimens is 1 μg/kg/day [4]. The iodine content of breast milk reflects maternal iodine status, and a small study in Scotland reported mean levels to be ~10 μg/dl [5]. A review of several UK manufactured formula brands (e.g. Comfort first infant formula, Cow & Gate Plus, Milupa Aptamil First, SMA Gold) found that none provided the recommended iodine intake of 90 μg/day at birth for term infants [6]. Parenteral nutrition and the iodine content of prescribed drugs and red blood cell concentrates together provided only 1-3 μg/iodine/day [5]. Neonates in the UK do not receive supplemental iodine as they are assumed to receive sufficient iodine from enteral and parenteral formula and/or breast milk. This assumption is probably incorrect, especially for infants receiving parental nutrition [7].

In addition to the risk of iodine deficiency, paradoxically, preterm infants are also vulnerable to the effects of iodine overload because the Wolff-Chaikoff effect, which blocks the uptake of excess iodine by the thyroid gland, does not mature until around 36-40 weeks' gestation [8]. Neonatal overload may occur through neonatal use of iodinated contrast media [9] and/or iodinated skin disinfectants [10], if there is maternal exposure via supplements or topical iodine use during pregnancy or delivery, and there is additional infant exposure if the mother breast-feeds [11]. A major source of neonatal exposure is from maternal exposure from the use of iodine-based skin disinfectants prior to caesarean section [12].

Several studies have confirmed neonatal thyroid dysfunction consequent to exposure to iodinated contrast media [13-15], but the results are inconsistent; one study found no evidence [16] of

transient hypothyroidism and another a rate of 75% [14]. The consequence of using iodine-based skin disinfectants is also variable, with rates of hypothyroidism reported from 0% [17,18], 20% [19], 25% [10], to 78% [14].

Recent systematic reviews considered neonatal exposure to iodinated contrast media [20] and to topical iodine [21]. Both reviews concluded that the studies appraised were affected by bias but nevertheless neonates exposed to iodinated contrast media and topical iodine appeared to be at risk of thyroid dysfunction and development of hypothyroidism. Preterm infants were identified at higher risk than term infants. Presumably in reflection of this inconsistent but scientifically rational evidence [22] the 2013-14 edition of the British National Formulary (BNF) for Children [23] states that use of topical iodine is contraindicated in neonates <32 weeks' postmenstrual age and infants <1.5kg, and regular use during pregnancy and while breast-feeding should be avoided. The equivalent American publication cautions that as iodine crosses the placenta it thus may cause hypothyroidism/goitre in the fetus and newborn [24]. There is no comment about iodinated contrast media, as it is not a listed drug. However, guidance leaflets included with contrast media (e.g. Optiray 300-GB TL -05/2009) recommend monitoring thyroid function 6-10 days and 1 month after administration because of the risk of hypothyroidism due to iodine overload.

The aim of this study was to determine whether exposure to topical iodine or contrast media was associated with grossly altered thyroid function as reported by the earlier studies [14].

METHODS

Infants <32 weeks' gestation were recruited between 2007 and 2012 from five neonatal intensive care units in the UK (two in Scotland and three in England); our aim was to recruit infants consecutively. The single exclusion criterion was serious congenital anomaly. Written informed consent was obtained from all mothers. The study was approved by Medical Research Ethics Tayside Committee (A), 06/S1401/116.

This study compared infants categorised as either exposed or unexposed to topical iodine (maternal or neonatal use) and/or iodinated contrast media. Special care was taken by study nurses to record maternal exposure to iodine during pregnancy and parturition, dosage and type of neonatal exposure to contrast media, and the use of iodine-based skin disinfectants. Exposure was classified as 1) to neonatal contrast media only, 2) to topical iodine prior to caesarean section only, 3) as mixed exposure and 4) unexposed. Exposure was confirmed by cross-checking obstetric and neonatal clinical records. Neonatal exposure data were collected prospectively by staff actively involved in the care of neonates and the study; obstetric data were collected retrospectively but the majority of mothers delivered in the same hospital as the neonatal unit, and obstetric policy regarding iodine use for skin disinfection is standard for all personnel in the unit.

The main outcome measures were levels of thyrotropin (TSH) and thyroxine (T4) measured on postnatal days 7, 14, 28 and at the equivalent of 36 weeks' gestation. Heel-prick blood was spotted onto filter-paper card and posted immediately to the Neonatal Screening laboratory, Academic Medical Centre, Amsterdam. The Dutch screening program for congenital hypothyroidism is primarily based on T4 measurement in filter paper but measurements of TSH and TBG (thyroid binding globulin) are also performed. T4 levels are also expressed as a standard deviation (T4 sd) of the daily mean i.e. z score; levels ≤-3.0 are considered abnormal. Assays were performed according to the manufacturer's protocol: total T4 by fluoro immunoassay (AutoDelfia, Perkin Elmer, Waltham, MA) and TSH by an immunometric assay (Brahms, Thermo scientific, Henningsdorf, Germany). Analysis of the blood-spot cards within the screening laboratory ensured that all suspect results were quickly notified to the neonatal unit and local diagnostic tests and treatment protocols instigated. We classified TSH levels ≥6mU/L as the threshold of suspicion, as this is the lowest level of TSH to prompt recall for repeat testing used by a UK newborn screening laboratory for congenital hypothyroidism. Suspect levels were faxed to FLRW, who alerted the appropriate duty neonatal consultant. Hypothyroidism was classified if treatment with Levo-thyroxine was required; hyperthyrotropinaemia was classified as levels of TSH between 10.1 and 19.9 mU/L.

Clinical and demographic data were recorded from birth for 28 days; although a final blood sample was taken at the equivalent of 36 weeks' gestational age. Data recorded included: gestation at birth, birth weight, birthweight ratio (infant weight standardised to national data), gender; and on postnatal day 7, 14 and 28: type and quantity of nutrition; prescribed drug usage, neonatal illnesses/conditions, and level of nursing care required (as a proxy of illness severity) [25].

Mean levels of TSH and T4 were calculated for infants grouped by source of iodine exposure for each day of blood sampling (± a day). (Infants were only sampled once if their day 28 blood was within a day of their 36 weeks' blood.) Differences in mean levels between the exposed and unexposed groups were found using, as appropriate, the *t* test for unequal variance or Fisher Exact test. Univariate general linear models were used to evaluate TSH levels on days 7, 14 and 28 and exposure group adjusted for gestational age, level of nursing care required, birthweight ratio, gender, and drug usage. We collected information about the use of dexamethasone, dopamine and caffeine as these drugs can inhibit neonatal TSH secretion [26]. The target sample was 200 infants which would give 80% power, p=5%, to detect an incidence of hypothyroidism of 25% in the exposed group.

RESULTS

Of the 173 infants in the study, 125 were exposed to extraneous iodine and 48 were unexposed (other than to dietary iodine contained in breast milk or added by manufacturers to formula milk). No infant was exposed to topical iodine for neonatal skin antisepsis; the most frequent exposure source was neonatal contrast media (Table 1).

Thirteen infants recorded a level of TSH ≥6mU/L at one of the blood sampling days (Table 2); 6% (6/95) of infants exposed only to contrast media, 19% (3/16) infants exposed only to maternal topical iodine, and 8% (4/48) of the unexposed group (Tables 1 and 2). Overall the incidence of thyroid dysfunction (TSH≥6mU/L) in our exposed cohort was 7.2%, and 8.3% in the unexposed cohort. No infant was diagnosed with hypothyroidism; three infants had transient

hyperthyrotropinaemia and all were from the exposed group. Five infants who had TSH ≥6 mU/L, all from the exposed group, had a T4 z score ≤-3.0; the T4 levels in four infants normalised by 36 weeks and one infant died.

Contrast media for verification of central venous catheter position was the most common source of iodine exposure (Table 1). Three types of media were used: Optiray 300, Omnipaque 240/250 and Ultravist 300. Doses ranged from 0.2-1.0ml per application, with a mode of 0.3ml. One-hundred-eight infants were exposed to contrast media; Ultravist 300 was the most commonly used (52%), followed by Omnipaque 240 (32%), Optiray 300 (15%) and Omnipaque 250 (1%). Eighty-six infants received a single dose of media, 18 infants received two doses of media and 4 infants received 3 doses of media. The median day for receipt of the 1st , 2nd and 3rd doses of contrast media were, for the mixed exposure group, 3, 57 and 65 days post birth; while for the contrast only exposure group the medians were 3, 17 and 21 days respectively. Twenty-one infants were exposed to topical iodine. The majority of infants received maternal breast milk during the first 28 days postnatal. Generally, breast milk provided the majority of the nutritional intake (Table 3).

Compared to the unexposed infants, infants exposed to iodine via caesarean section had significantly higher TSH and T4 levels on postnatal days 7, 14 and 28 (TSH only); although by the equivalent of 36 weeks' gestation, TSH and T4 levels between the groups did not differ (Table 4). Regression analyses confirmed the associations between TSH levels on days 7, 14 and 28, and iodine exposure from caesarean section; associations which persisted after adjustment for confounding factors (Table 5).

Compared to unexposed infants, the mean gestational age at birth for the infants exposed only to contrast media and the mixed exposure group was significantly lower, and this is reflected by lower mean birthweights in these groups (Table 3). There were 6 neonatal deaths, three in the contrast media only group and three in the unexposed group. There were no differences in the levels of illness experienced by the groups of infants (Supplementary Table 1). Neonatal dexamethasone and

dopamine was used in less than 1.5% of infants: for the exposed group (respectively 1.1% and 1.3%) and unexposed group (0.7% and 0%); caffeine (Table 3) was used for 69.3% of the exposed and 50.0% of the unexposed group.

The number of infants with missing neonatal blood data was low (range 0-14%), for all exposure groups. By 36 weeks the amount of missing data was higher (range 20-43%) particularly for the caesarean section only and mixed exposure groups (Table 4). We did not monitor missed infants and estimate that we recruited 60% of eligible infants (Supplementary Table 2).

DISCUSSION

This study aimed to determine whether the incidence of thyroid dysfunction following iodine exposure was as high as the 75-78% previously reported [14]. We found an incidence of thyroid dysfunction (TSH≥6mU/L) in the exposed group of 7.2%, and 8.3% for the unexposed group.

Quantitative information about the iodide content of contrast media is sparse. Iodinated contrast media contain variable but large amounts of bound iodide (biologically inactive), which liberate variable amounts of (biologically active) free iodide [16]. Manufacturers of contrast media do not specify the free and bound proportions of iodide used in their product sheets, and the amount of free iodide is likely to vary between and within manufacturers [14,27]. A single dose of Omnipaque contrast media (with a small application of topical iodine for skin cleansing) was estimated to expose an infant to 243 μg/kg of free iodide [14]. Another study reported a content range, for various media (including Omnipaque), of 2-21 μg/ml [27]. Precise information about the actual dose of free iodide that an infant is exposed to is further confused by the *in vivo* degradation of iodide, which increases the biological load. The most commonly used contrast media in our cohort was Ultravist 300 at a modal dose of 0.3ml i.e. 90mg of iodine. If we assume 21 μg/ml [27] is representative of the free iodide content of the contrast media used in our study, it suggests that our infants were exposed to about 6 μg/iodide per dose, which could explain why so few of the infants showed marked thyroid dysfunction.

Quantitative information about the free iodide content of topical iodine solutions is also not readily available. Furthermore, although the placenta can store iodine and perhaps protect the fetus from deficiency [28], is it is not clear how infants become exposed to iodide from caesarean section and/or epidural anaesthesia. It could be via the blood directly, as iodide also crosses the placenta [22], but a more substantive source is likely to be breast milk, as iodide is actively concentrated in the breast [29].

Monitoring exposed infants will undoubtedly reveal high levels of urinary iodide [21], but increased levels do not establish definitive proof that the thyroid gland has been adversely affected. The assays measuring urinary iodine cannot distinguish between bound iodide and free iodide, and it is only the latter that is taken up by the thyroid gland [30]. Furthermore comparatively few infants exposed to iodine and with high levels of urinary iodide, actually exhibit thyroid dysfunction [15]. There are many other unknown facts. For instance, the relationship between urinary/serum iodide levels and thyroid function is unclear; infants exposed to the same quantities and types of contrast media show different thyroid responses and urinary iodide levels; and, exposure to contrast media and/or topical iodine can raise urinary iodine levels >1000-fold yet remarkably few exposed infants show thyroid dysfunction [15]. Because of this ambiguity, we elected not to measure urinary/serum iodide levels in our exposed infants. We assumed that iodine exposure had occurred based on the circumstantial evidence provided by the previous research [13-15], and the cautionary notes of the contrast media manufacturers and BNF [23].

Our findings are generally quite different from those reported previously [9-11,14,19,29] and from the conclusions drawn by systematic reviews of exposure via contrast media [20] and povidone-iodine [21]. How authors define and measure thyroid dysfunction may explain some of the disparity between studies. Many authors either omit a definition or describe hypothyroidism using only clinical terminology [9,10,18]; others imply use of a quantified cut-off [14,15,19,29]; but very few set out a clear definition in their methods [17]. Recent guidelines [31] state that venous TSH levels

>20mU/L, with or without low, age-adjusted, FT4 levels, should be the threshold for thyroxine treatment. As TSH levels in whole blood are about one-half those in serum, it maybe that our definition of hyperthyrotropinaemia is unduly strict and will under report infants with thyroid dysfunction. We did not measure FT4, although we did have (total) T4 measurements. However interpretation of neonatal T4 measurements, especially in a preterm population, is complex – affected by the ontogeny of thyroid hormones, time of testing [32], sickness levels, the action of drugs such as dopamine, dexamethasone and caffeine [18,26,33] and lack of reference range data for whole blood measurements. Using the T4 z score provided by the screening laboratory helps a little, as it is calculated on a daily basis and reflects the population sampled on that day. Nevertheless, preterm infants by the nature of their preterm birth are going to fall in the far left of the distribution curve. Our definition of hypothyroidism, however, reflected clinical practice as we classified hypothyroidism pragmatically on the basis of requiring Levo-Thyroxine treatment, and units followed their routine clinical protocols guided by locally taken and analysed thyroid function tests.

Our study has several strong features. With the exception of screening recall studies, our study is the largest, gestational-age relevant, prospective case-comparison study undertaken. It uses a contemporary population and adjusted for the key potential confounding influences of TSH, such as drug usage and illness. Our definition of thyroid function was agreed *a priori.* Infants were followed for 28 days postnatally and then again at the equivalent of 36 weeks' gestation. The gap between neonatal thyroid monitoring and the equivalent of 36 weeks' gestation is, by definition, greater the earlier the gestational age at birth i.e. the very infants who are at most risk of thyroid dysfunction due to exposure. It is possible that the confirmatory normal TSH levels at 36 weeks' gestation which were found for all infants, masked transitionally high TSH levels during the weeks when no measurements were undertaken.

Our study has some limitations. We have assumed iodine exposure occurred. The contrast media and topical iodine used in our study hospitals have been reported in other studies to be associated with greatly elevated urinary iodide levels and, in the absence of any change in manufacture, we believe the infants in our study will also have been exposed to similar levels of free and bound iodide. Our study has an element of recruitment bias; although we aimed for consecutive recruitment, some infants were missed and our population was skewed to the older gestations, which has the effect of attenuating any relationship between iodine exposure and neonatal thyroid outcome. We estimate that we might have missed 40% of eligible infants, so even if all the missed infants had thyroid dysfunction we would still report an incidence of well below the 78-80% reported previously [14]. Our exposure source was biased towards contrast media, with relatively few infants exposed to topical iodine. While we collected information about drug usage that may affect levels of TSH and thyroid hormones, we did not collect any information about renal function, impairment of which can affect clearance of iodine which may in turn impact the risk of developing hypothyroidism.

The BNF cautions against the use of topical iodine in preterm infants and in women during pregnancy and breast feeding, and manufacturers of contrast media recommend monitoring thyroid function after administration because of the risk of hypothyroidism due to iodine overload. The use of contrast media for neonates is widespread and one study reported its use in 64% of UK neonatal units [34]. The use of topical iodine is not well recorded and its use in UK neonatal units has possibly decreased from around 21% in 2006 [21] to 1% in 2013 [35] as units move to chlorhexidine gluconate for skin antisepsis. Use of topical iodine in obstetric units is also poorly recorded and one survey found it was used in 57% of obstetric units [21]. However, obstetric and neonatal surgical applications of topical iodine is likely to be more harmful to the preterm infant than neonatal skin cleansing prior to catheter placements, because the quantity of topical iodine used per application for skin cleansing prior to caesarean section or epidural or neonatal surgery is much greater than for neonatal catheter positioning.

From the results of this study it is not possible to say unequivocally that exposure causes no harm; although the incidence of thyroid dysfunction as a result of exposure to iodinated contrast media is very unlikely to be near the high level reported by L'Allemand et al [14]. But, even with our perhaps over strict definition of thyroid dysfunction, several infants in our study had transient thyroid dysfunction, which is associated with neurodevelopmental compromise [34]. The best evidence to date is from the systematic reviews which indicate that neonatal thyroid dysfunction is present in around 18-20% of exposed infants [20,21]. A randomized controlled trial is needed to determine unequivocally whether exposure to extraneous iodine causes thyroid dysfunction. In the meantime, clinicians can debate or act on the advice of the BNF [23], the American Pharmacists Association [24], and the manufacturers of contrast media. (Chlorhexidine or octenidine are alternatives to topical iodine, although also hold risks for preterm infants [36].) However, until research is unequivocal it is imperative that all preterm infants exposed to extraneous iodine have their thyroid function monitored, for a sufficient period as per the manufacturers' advice, post exposure. Clinical guidelines, which define cut-offs for normal TSH and (F)T4 levels, and which are relative to the gestational and postnatal age of the infant and the blood media used, are a priority.

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TABLE 1 SOURCES OF NEONATAL EXPOSURE TO IODINE

Sources of iodine exposure	
Single exposure source	
• Neonatal contrast media	N=95
• Topical iodine prior to caesarean section	N=16
Mixed exposure source	
• Maternal use of vitamins containing iodine and neonatal contrast media	N=9
• Topical iodine prior to caesarean section and neonatal contrast media	N=4
• Neonatal use of iodine based eye-drops and possible maternal vitamins containing iodine use	N=1
Unexposed	N=48

TABLE 2 ROUTES*OF EXTRANEOUS IODINE EXPOSURE, GESTATIONAL AGE, POSTNATAL TSH AND T4 LEVELS AND DATE OF DEATH IN INFANTS WHO RECORDED TSH LEVELS ≥6MU/L

Infant	Gestation (weeks + day)	Route and day of exposure	TSH mU/L day 7	T4 z score day 7	TSH mU/L day 14	T4 z score day 14	Route and day of exposure	TSH mU/L day 28	T4 z score day 28	TSH mU/L 36 weeks**	T4 z score 36 weeks**	Week of death if applicable
1	28 + 5	C/S	8	-2.1	3	-1.8		5	-2.4	4	-1.7	n/a
2	29 + 1	C/S	6	-1.4	7	-2.5		7	-1.4	missing	missing	n/a
3	28 + 6	C-M d3	10	-3.1	2	-2.1		11	-3.4	4	-2.9	n/a
4	31 + 2	C-M d6	9	-3.3	3	-1.9		4	-1.8	4	-1.3	n/a
5	30 + 1	C/S	2	-2.5	7	-2.1		2	-2.5	2	-1.8	n/a
6	24 + 6	C-M d3	1	-3.8	8	-2.7	C-M d17	1	-3.0	n/a	n/a	Equivalent of 32 weeks' gestation
7	27 + 4	C-M d3	1	-3.2	10	-2.4		5	-3.9	4	-1.7	n/a
8	28 + 0	C-M d2&3	1	-3.8	25	-3.2	C-M d20	1	-3.0	3	-2.4	n/a
9	29 + 5	C-M d0	3	-2.4	6	-2.8		missing	missing	missing	missing	n/a
Unexposed infants												
1	31 + 1		2	-1.2	8	-1.3		2	-1.9	2	0.4	n/a
2	28 + 0		2	-2.0	6	-1.9		2	-1.9	2	-1.2	n/a
3	30 + 2		4	-2.2	5	-2.5		6	-2.5	4	-1.3	n/a
4	31 + 1		1	-2.0	1	-2.3		6	-1.2	1	-1.6	n/a

C/S caesarean section C-M contrast media for placement of central venous catheters

* No infant was exposed to iodine for skin disinfectant prior to placement of long line or surgery

**36 weeks refers to the week of gestation that the preterm infant would have been in had they remained *in utero*

TABLE 3 INFANT AND MATERNAL CHARACTERISTICS

	EXPOSED						UNEXPOSED	
	caesarean section only N=16		contrast media only N=95		Mixed exposure N=14		N=48	
	Mean	**(SD)**	Mean	(SD)	Mean	(SD)	Mean	(SD)
Gestation (weeks)	29.6	(1.5)	28.2	(1.9) [a]	27.1	(2.6)[aa]	29.2	(2.0)
Birth weight (g)	1437	(329)	1154	(326)[b]	948	(262)[bb]	1329	(333)
Birthweight ratio	1.1	(0.2)	1.0	(0.2)	0.9	(0.2)	1.0	(0.2)
Maternal thyroid disease								
Yes	0		7 (7%)		0		3 (6%)	
No	16 (100%)		85 (90%)		13 (93%)		43 (90%)	
missing data	0		3 (3%)		1 (7%)		2 (4%)	
Nutrition on day 7	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
breast milk (ml)	143	(92)	52	(59)	48	(98)	104	(99)
formula milk (ml)	62	(79)	3	(18)	17	(43)	44	(77)
total (ml)	216	(45)	170	(54)	160	(95)	198	(56)
Nutrition on day 14								
breast milk (ml)	174	(133)	116	(93)	80	(78)	126	(112)
formula milk (ml)	89	(121)	15	(44)	41	(82)	71	(102)
total (ml)	263	(54)	185	(55)	147	(43)	216	(59)
missing data			3				2	
Nutrition on day 28								
breast milk (ml)	127	(162)	176	(114)	91	(84)	129	(131)
formula milk (ml)	198	(163)	34	(84)	74	(120)	133	(150)
total (ml)	325	(73)	236	(70)	177	(65)	268	(78)
missing data	2		7				10	
Gender								
female	7 (44%)		48 (51%)		5 (36%)		18 (38%)	
male	9 (56%)		47 (49%)		9 (64%)		30 (63%)	
Caffeine day 7								
yes	6 (38%)[c]		81 (85%)		11 (79%)		34 (71%)	
no	10 (63%)		14 (15%)		3 (21%)		14 (29%)	
Caffeine day 14								
yes	3 (19%)[d]		83 (87%)[dd]		12 (86%)		25 (52%)	
no	13 (81%)		10 (11%)		2 (14%)		21 (44%)	
died	-		2 (2%)				2 (4%)	
Caffeine day 28								
yes	1 (6%)		55 (58%)[e]		8 (57%)		13 (27%)	
no	15 (94%)		35 (37%)		6 (43%)		30 (63%)	
died	-		3 (3%)		-		3 (6%)	
missing data	-		2 (2%)		-		2 (4%)	

[a] compared to unexposed t=2.87, p=0.005 [aa] compared to unexposed t=2.79, p=0.013

[b] compared to unexposed t=3.00, p=0.003 [bb] compared to unexposed t=4.49, p=0.0001

[c] compared to unexposed, Fisher exact p=0.04 [d] compared to unexposed, Fisher exact p=0.03

[dd] compared to unexposed, Fisher exact p=0.00002 [e] compared to unexposed, Fisher exact p=0.002

TABLE 4 DIFFERENCES IN MEAN LEVELS OF TSH AND T4 IN HEEL PRICK BLOOD ON POSTNATAL DAYS 7, 14 AND 28 AND EQUIVALENT OF 36 WEEKS' GESTATION ACCORDING TO SOURCE OF EXPOSURE

	Caesarean section only				Contrast media only				Mixed exposure				Unexposed			
	day 7	**day 14**	**day 28**	**36 wks**	**day 7**	**day 14**	**day 28**	**36 wks**	**day 7**	**day 14**	**day 28**	**36 wks**	**day 7**	**day 14**	**day 28**	**36 wks**
TSH mean	2.87 [a]	3.19 [a]	3.14 [a]	2.13	1.50	1.98	1.67	1.72	1.83	1.43	1.86	2.0	1.69	2.07	1.87	1.71
mU/L s.d.	2.03	1.80	1.66	1.13	1.39	2.86	1.47	1.05	1.03	1.09	1.17	1.0	0.97	1.61	1.32	0.89
n sampled	15	16	14	8	88	90	81	74	12	14	14	9	45	44	38	35
n available*	16	16	14	14	95	93	92	92	14	14	14	14	48	46	42	42
T4 mean	44[b]	52[b]	48	59	32	39	43	51	29	36	31[c]	58	33	40	42	51
nmol/L s.d.	9.5	17.2	10.4	18.0	12.5	14.4	13.7	12.9	15.1	16.4	15.7	13.6	12.0	12.9	14.2	20.1
n sampled	15	16	14	8	88	90	81	74	12	14	14	9	45	44	38	35
n available*	16	16	16	16	95	93	92	92	14	14	14	14	48	46	42	42

[a] TSH levels caesarean section only compared to TSH levels unexposed: **day 7** p=0.05, **day 14** p=0.04, **day 28** p=0.02

[b] T4 levels caesarean section only compared to T4 levels unexposed: **day 7** p=0.001, **day 14** p=0.02

[c] T4 levels mixed exposure compared to T4 levels unexposed: **day 28** p=0.03

* the denominator of 'n available' takes into acccount the 6 infant deaths and 3 infants discharged, and the age at death/discharge

TABLE 5 REGRESSION ANALYSES OF EXPOSURE TO IODINE ON TSH LEVELS ADJUSTED* FOR CONFOUNDING VARIABLES

TSH level on day 7	Effect estimate	Standard error	t	P value
Iodine exposure group				
Caesarean section only	0.888	0.277	3.203	0.002
Mixed exposure	-0.042	0.312	-0.134	0.894
Contrast media only	-0.313	0.168	-1.859	0.065
unexposed	reference			
Nursing level of care				
Level 1 (highest level)	-0.314	0.212	-1.482	0.141
Level 2 and 3 (moderate/low)	reference			
Caffeine prescribed on day 7				
Yes	0.066	0.179	0.370	0.712
No	reference			
Infant gender				
Male	-0.178	0.143	-1.250	0.213
Female	reference			
Gestational age	-0.023	0.047	-0.485	0.628
Birth weight ratio	-1.265	0.418	-3.030	0.003
TSH level on day 14				
Iodine exposure group				
Caesarean section only	1.745	0.800	2.182	0.031
Mixed exposure	-1.360	0.874	-1.556	0.122
Contrast media only	-0.640	0.523	-1.224	0.223
unexposed	reference			
Nursing level of care				
Level 1 (highest level)	1.338	0.704	1.902	0.059
Level 2 and 3 (moderate/low)	reference			
Caffeine prescribed on day 14				
Yes	0.845	0.567	1.491	0.138
No	reference			
Infant gender				
Male	-0.029	0.403	-0.072	0.943
Female	reference			
Gestational age	0.066	0.138	0.475	0.636
Birth weight ratio	-1.473	1.188	-1.240	0.217
TSH level on day 28				
Iodine exposure group				
Caesarean section only	1.282	0.365	3.509	0.001
Mixed exposure	-0.572	0.384	-1.490	0.139
Contrast media only	-0.252	0.231	-1.089	0.278
unexposed	reference			
Nursing level of care				
Level 1 (highest level)	-0.594	0.372	-1.596	0.113
Level 2 and 3 (moderate/low)	reference			
Caffeine prescribed on day 28				
Yes	-0.330	0.237	-1.393	0.166
No	reference			
Infant gender				
Male	0.007	0.186	0.040	0.968
Female	reference			
Gestational age	-0.203	0.074	-2.722	0.007
Birth weight ratio	-1.839	0.557	-3.303	0.001

*** Dexamethasone and dopamine usage were not used in the regression model as so few infants received these drugs.**