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Iodine Intake, Thyroid Function and Neurodevelopmental Outcome in Preterm Infants from 24 to 30 Weeks Gestation

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Abstract

Neonatal hypothyroxinemia has been linked to increased risk of neurodevelopmental disabilities.

The objective is to evaluate iodine status and thyroid function of premature babies and to correlate the data with neurodevelopment at 2 years. 67 infants were enrolled. Gestational age in weeks (27.5±0.2) and weight (986.5±30.8 gr). Breast milk contained 25.8±1.4 µg I/100 ml and formulae were 10 µg I /100 ml. Only 20% of the babies had an iodine intake above 30 µg I/Kg. Thyroid hormones were negatively correlated by a low iodine intake. There were differences in neurodevelopmental indexes with lower iodine intake. Iodine intake should be ensured during the neonatal period by breast milk or preterm formulae with high iodine content.

Keywords: Hypothyroxinemia; Preterm infants; Thyroid; Neurodevelopment; Iodine deficiency

Abbreviations

ICCIDD: International Council for Control of Iodine Deficiency Disorders; TSH: Thyrotropin; T4: thyroxine; T3: 3,5,3′-Triiodothyronine; Tg: Thyroglobulin; TBG: Thyroid Binding Globulin; GA: Gestational Age in weeks; BW: Body Weight; ELBW: Extremely Low Birth Weight babies; SD: Standard Deviation; SE: Standard Error

Introduction

Iodine deficiency is a major cause of preventable mental retardation. The minimum Recommended Dietary Allowance (RDA) for different age groups was revised in 2007 by the International Committee for the Control of Iodine Deficiency Disorders (ICCIDD). Premature babies need at least 30 µg I/kg/day [1-3]. The iodine content of formulae for premature new-borns should be 20 µg I/dL and that of starting formulae, at least 10 µg I/dL. When feeding with breast milk is not possible, the infant might be iodine deficient due to the low iodine content of the formulae [4-13].

Thyroid hormones (thyroxine or T4 and 3,5,3'-triiodothyronine or T3) play a crucial role in neurodevelopment during intrauterine development (16). Throughout pregnancy the mother contributes to a significant extent to the pool of fetal T4 and at term, about 30-50% of circulating T4 in the fetus is from maternal origin. Therefore, premature infants, have transient hypothyroxinemia due to the loss of maternal supply, in addition to immaturity of the thyroid axis [14,15]. Hypothyroxinemia of prematurity is most frequent in infants born extremely early with very low birth weight [16-20] and neonatal illnesses (e.g. bronchopulmonary dysplasia, intraventricular hemorrhage or periventricular leukomalacia) [21-23]. Many studies support the hypothesis that hypothyroxinemia, even if transient, is linked with to poorer motor and cognitive outcomes in infants born before term [24-29]. An adequate iodine intake should be ensured in preterm infants, but even if the iodine supply is adequate, it may not be sufficient to avoid hypothyroxinemia.

The purpose of this study was to measure iodine intake, iodine excretion and serum T4, FT4, TSH, T3 and thyroglobulin at different ages in infants born 24-30 weeks of gestation and correlate the data with their long term neurodevelopment.

Materials and Methods

We included a cohort of mothers and infants delivered at 24-30 weeks gestation. We recluted 67 infants, but 8 died during the study period. The study was performed at University Hospital La Paz, Madrid (Spain), a tertiary referral center with approximately 10,500 deliveries per year. Inclusion criteria were: infants born below 30 weeks of gestation during 2005. Exclusion criteria from the study were major congenital abnormalities and mothers with endocrine disease.

Infant samples were obtained between 3-7 days during the first week of life and then at 14, 21, 30 days and at discharge. Every infant contributes to the hormone measurements each time point. In order to eliminate the confounding effect of topical iodine use, all iodine-containing antiseptics were banned from the neontal unit and no iodinated contrast media were used for central venous catheter positioning. Also, topical iodine was not used as a maternal skin disinfectant prior to delivery by Caesarean section or insertion of epidural analgesia. Iodine content was determined in samples of the different formulae or the maternal milk given to each baby and the ingested volume over a 24 h period was recorded in each case. Urine samples were collected at each study period. The urine samples were obtained from cotton wool balls placed in the diapers and from clean catch specimens in a urine collection bag. The iodine concentration

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Table 1: Data showing iodine content of maternal and formula milk, iodine intake and urinary iodine excretion in 67 preterm infants at 24-30 weeks gestation at different postnatal ages (mean +/- SD).

	1st sample	2nd sample	3rd sample	4th sample	5th sample
Number of Babies	54	55	52	49	6
Age in days	0.3 ± 0.0	9.1± 0.5	18.5 ± 0.7	28.4±1.0	28.7± 0.7
Gestational age (weeks)	27.0±0.25	28.9±0.2	30.3±0.2	31.8±0.27	31.6±0.6
Weight (gr)	987.0±30.9	938.7±30.0	1035.9±34.4	1221.5±50.3	1196.6±34.7
Height (cm)	35.3± 0.4	36.1 ±0.1	36.6± 0. 3	38.6±0.42	40.5 ±2.5
Iodinecontent in formula (micrograms /100 ml)	-	12.5± 0.7	12.4 ± 0.7	13.4 ± 0.7	12.6± 0.7
Iodine content in breastmilk (micrograms/100 ml)	-	24.4± 2.0	23.6± 1.8	22.5± 1.3	26.8± 7.1
Volume of Formula (ml)	0	61.8±8.4	113.1±11.0	161.4±12.5	-
Volume of Breast milk (ml)	0	73.0±11.5	115.7±17.3	122.8±18.4	198.0±42.0
Iodine intake with formula	<3	6.0±1.0	15.0±1.7	19.5±2.4	
Iodine intake with breastmilk	<3	23.9± 7.3	32.8±7.2	25.4±5.0	45.7±12.7
Total Iodine intake (µg I /day)	0.2±0.1	13.8 ±3.0	23.5±3.1	23.6±2.0	45.7±12.7
Urinary iodine (µg I / Kg/ day) Mean± Standard deviation	138.9±117.1	225.8±166.9	188.9±99.7	188.9±99.7	-
% of infants with urinary iodine below 100 µg I / Kg/ day	47.4	29.2	22.7	22.7	-

was determined using a modification of the method described by Benotti and Benotti for serum [30]. Venous blood samples were withdrawn for the determination of serum concentrations of Thyroid Stimulating Hormone (TSH), total T4, free T4 (FT4), T3, Thyroxine-Binding Globulin (TBG) and thyroglobulin (Tg): all were measured by specific enzyme immunoassay (ROCHE Diagnostics). Infants on current standard regimens of total parenteral nutrition have a mean iodine intake of lessthan 3 µg/kg/d. The manufacturer's recommended dosage for infants is 1 mL/kg/d of PeditraceR parenteral solution, which contains 1.3 g/mL potassium iodide equivalent to 1 µg iodide/ kg/d [31-33].

Families were invited to participate in the follow-up programmes that consisted of a battery of developmental, neurologic and behavioural assessments at 6 to 24 months' corrected age. There were 47 infants who completed the follow-up period. 11 infants were lost due to changes in address city and refusal to come back to the hospital.

The primary outcome was neurodevelopmental status at 2 years' corrected (for prematurity) age. Babies who are born prematurely often have two ages: Chronological age is the age of the baby from the day of birth-the number of days, weeks or years old the baby is. Adjusted age is the age of the baby based on his due date. Health care providers may use this age when they evaluate the baby's growth and development.

Neurodevelopmental testing was performed with Brunet-Lezine test and Bayley Scales of Infant Development II (BSID-II) obtained at an adjusted age of 6 months to 2 years [31,32]. Both tests were administered by the same certified examiner with previous formal training.

Secondary outcomes were blood levels of total and free T4 and T3, TSH, Tg and TBG. Illness type and severity are also recorded, i.e. necrotising enterocolitis, persistent ductus arteriosus, respiratory distress (days of endotracheal intubation, days of continuous positive airways pressure), chronic lung disease (the need for oxygen at 36 weeks' corrected age), cranial ultrasound changes, acquired infection and vision impairment. Postnatal drug use (e.g. dexamethasone, dopamine, insulin, caffeine and indomethacin) and nutritional status.

The study was approved by the University Hospital La Paz Research Ethics Committee; in all cases written informed consent was obtained.

Statistical methods

Data are given as mean and SD and they are normally distributed. Data were subjected to one-way analysis of variance, after testing for homogeneity of variance. The significance of the difference between groups was identified by the Newman-Keuls test for multiple comparisons. All anayses and multiple regression and partial correlation analyses were performed using the SPSS program. Whenever it is stated that a certain variable was higher or lower, for different groups or that correlations existed between the variables, it is implicit that the differences or correlation coefficients. $P<0.05$ were considered as statistically significant.

Results and Discussion

Infants

A total of 67 infants were included in the study. An elevated proportion (39%) was born from multiple births. The main characteristics, including gestational age in weeks (27.5±0.2), weight (986.5±30.8 gr), height (35.4±0.4 cm) and head circumference (25.2±0.3). 31 infants (45%) were born before week 28.

There was a high incidence of cardio-respiratory disease (respiratory distress syndrome (45 infants) and episodes of apnea (50 cases) treated with caffeine). In 30 cases blood transfusion was needed and antibiotics were administered in 39 cases. 45 infants received parenteral nutrition. Other conditions included hypotension, treated with dopamine (34 cases), hyperglucemia, treated with insulin (13 cases), sepsis (17 cases) and ductus arteriosus (12 cases) treated with indomethacin. Neurological lesions were present in 28 cases

Table 2: Thyroid hormones, TSH, TBG and Tg profile in preterm infants.

Percentiles		5	10	25	50	75	90	95
< 7 days	T3 (nmol/L)	0.5	0.6	0.79	0.8	1.3	1.6	1.8
	fT4 (pmol/L)	10.9	11.8	14.2	16.4	20.4	29.6	36.6
	Tg (ng/dl)	23.4	32.9	41.1	64.6	104.0	120.2	192.1
	TSH (mUI/L)	0.9	1.3	2.0	5.0	7.5	11.7	19.0
	TBG (mg/L)	9.5	11.5	12.9	16.8	20.5	28.9	30.3
7-15 days	T3 (nmol/L)	0.7	0.8	0.9	1.2	1.6	1.9	2.1
	T4 (nmol/L)	22.4	29.5	51.2	79.6	102.9	119.7	150.9
	fT4 (pmol/L)	9.5	11.2	13.5	16.4	19.4	23.7	29.2
	Tg (ng/dl)	22.6	26.8	32.9	45.8	67.0	122.3	171.3
	TSH (mUI/L)	0.4	0.6	1.6	2.5	5.2	6.3	9.8
	TBG (mg/L)	12.6	13.9	16.0	19.3	24.8	29.9	31.0
15-30 days	T3 (nmol/L)	0.8	0.9	1.2	1.4	1.7	2.0	2.2
	T4 (nmol/L)	33.2	45.2	71.2	86.1	103.3	126.2	129.9
	fT4 (pmol/L)	11.3	11.8	13.3	15.4	18.0	21.9	24.5
	Tg 3 (ng/dl)	10.5	19.7	25.0	37.6	56.4	94.1	118.9
	TSH (mUI/L)	0.4	0.8	1.8	2.7	4.8	6.8	8.8
	TBG (mg/L)	12.5	14.7	19.1	22.1	27.7	30.9	34.8
30 days	T3 (nmol/L)	0.9	1.0	1.3	1.6	1.9	2.3	2.5
	T4 (nmol/L)	45.3	53.3	85.4	99.1	113.1	131.0	181.0
	fT4 (pmol/L)	11.3	11.6	13.0	14.5	16.4	22.2	23.9
	Tg (ng/dl)	12.5	16.7	24.1	31.1	55.0	95.7	127.9
	TSH (mUI/L)	0.6	1.01	1.7	2.4	5.1	6.3	7.8
	TBG (mg/L)	16.8	18.1	20.6	24.4	30.4	33.0	34.7
30-60 days	T3 (nmol/L)	0.6	0.6	1.1	1.5	2.3	.	.
	T4 (nmol/L)	62.6	62.6	67.4	82.8	98.4	.	.
	fT4 (pmol/L)	9.1	9.1	10.0	11.9	13.1	.	.
	Tg (ng/dl)	21.8	21.8	22.1	55.2	121.2	.	.
	TSH (mUI/L)	0.6	0.6	1.2	1.7	7.7	.	.
	TBG (mg/L)	16.8	16.8	18.9	24.3	27.4	.	.

(Intracraneal haemorrhage 18 cases, persistent leukomalacia 10 cases). Cerebral pathology was related to gestational age.

Iodine content in human milk and artificial formulae

The iodine content of breast milk was measured in 54 samples (Table 1). 13 mothers were not breastfeeding. Breast milk contained a mean of 25.8±1.4 µg I/100 ml (range 7.4-60). 76% of the milk samples had an iodine content of 10-30 µg I/100 ml. No statistically significant differences were found between samples of women at different gestational ages or between different times during the lactation period. The iodine content of 68 samples of formulae from 13 different brands used for feeding the infants was determined. In most preparations the average content was 10 µg I/100 ml, significantly lower than in human milk ($p<0.05$). Different types of formulae had different iodine contents.

Iodine intake

During the first week of life, all infants were on parenteral nutrition. As soon as they tolerate enteral feeding, the milk intake was increased. All infants were on enteral nutrition at 45 days.

The iodine intake of the premature babies was directly related to the iodine content of the milk and to the volume ingested daily. Tables show the iodine intake of all the infants at different postnatal ages. The babies do not ingest the recommended 150-200 ml/kg BW/day until 1 month of postnatal age and reach a weight of 2 kg or more. As a consequence of the small volume of milk ingested, the iodine intake of the infants was lower than the RDA. Only 20% of the babies had an iodine intake above 30 µg I/Kg during the first 30 days of life. However, the recommended iodine intake was reached by premature babies who received 50% or more of their food as breast milk.

Urinary iodine excretion and iodine balance

The daily urinary iodine excretion was calculated from the volume and the iodine concentration of the 24-hour urine sample and expressed per Kg of body weight (Table 3). Iodine excretion was higher than iodine intake during the first week, thus the infants were in negative balance. Many infants presented urinary iodine excretion

Table 3 panel A: Brunet-Lezine scores at 24 months.

Score	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound	Minimum	Maximum
Verbal	51.05	9.60	1.55	47.90	54.21	34	72
Motor	52.78	8.77	1.38	49.97	55.58	36	78
Numeric	50.47	7.46	1.21	48.02	52.93	31	64
Memory	43,08	7.59	1.23	40.58	45.58	30	59
Oculo motor coordination	53.75	10.08	1.59	50.53	56.97	36	78
Adaptative/ postural	0.93	1.42	0.22	0.47	1.38	0	5
Mental age	53097	6.32	1.04	51.86	56.08	39	64
Global intelligence	102,08	12.40	2.01	98.00	106.16	77	127

Table 3 panel B: Bayley Scales of Infant Development-II (BSID-II) score was assessed at 6, 9, 12, 18 and 24 months for all the infants. Indexes were Mental Developmental Index (MDI) and Psycho-Motor Developmental Index (PID) scale in study subjects.

PID index					MDI index			
Months	Mean	SE	Lower Bound	Upper Bound	Mean	SE	Lower Bound	Upper Bound
6	83.11	3.22	76.61	89.62	84.31	2.61	79.03	89.58
9	91.11	2.15	86.77	95.46	90.31	2.35	85.55	95.06
12	94.38	1.86	90.64	98.13	97.95	1.86	94.18	101.72
18	97.00	2.23	92.47	101.52	99.31	2.00	95.25	103.36
24	101.54	2.06	97.38	105.71	102.26	1.85	98.51	106.01

below 100 µg I/kg/day considered as a marker of iodine deficiency (from 47.4% during the first week to 22.7% at 30 days) (Table 1).

Thyroid function

The mean total T4 for infants was 80.7±2.6 nmol/L. Thirty percent of the babies had circulating total T4 below 2 SD of the mean value for their age and 12% of the babies had circulating free T4 below 2 SD of the mean value for their age, which can be considered as severe hypothyroxinemia (Table 2 shows the thyroid function profile). We studied the possible relationship between circulating parameters of thyroid function and iodine intake. Serum FT4, T3, Tg and TSH of preterm neonates were negatively correlated, independently of age, by a low iodine intake. Circulating T4 and T3 were lower in those infants with a lower iodine intake during the first 30 days of life ($p<0.05$).

Mental Development Scores (MDS)

The partial quotients are in the following areas of test Brunet-Lezine: Postural and motor control, oculo-motor coordination and adaptive behaviour to objects; Language and Sociability. The babies were classified according to the degree of neurological damage based on the score on overall IQ (QT) and WHO standards as follows: Profound damage (0-20), Severe damage (21-35), Moderate damage (36-50), mild damage (51-68), minimal damage (68-86), Normal (86-100), High (>100). Thirty four percent of children reached a score of lessthan 68 at 6 months, 15.8% at 9 months, 6.25% at 12 months and 6.6% at 18 months. At 24 months all children were above this score as shown in (Table 3 panel A).

Bayley Scales were assessed at 6, 9, 12, 18 and 24 months. Indexes were Mental Developmental Index (MDI) and Psychomotor Developmental Index (PID). Normal values are 100±15. Univariable and multivariable linear regression analyses were used to determine if there was a dose-related association between neonatal variables, iodine intake, thyroid hormones and neurodevelopmental outcomes. To evaluate primary outcomes, indexes were analyzed adjusting to neonatal pathology, drugs and gestational age. Data of Bayley scores are shown in (Table 2 panel B).

Children's scores on Brunet-Lezine and Bayley II Cognitive Scale were compared using statistical tests. MDI and PDI of BSID-II correlated to the Brunet-Lezine scores at early ages 6 to 18 months ($P<0.05$). Bayley II scores were significantly higher than Brunet-Lezine scores for preterm toddlers combined and separately at 24 months of age ($p<0.001$).

Correlation of neurodevelopmental indexes with iodine intake

There were significant differences in neurodevelopmental indexes among groups of infants of the same age who presented lower iodine intake. At 6, 9 and 12 months subjects with motor, oculomotor coordination, language and global scores IQ under 85 had a lower iodine intake (10 *vs* 30 µg, $p<0.05$) during the first month than children with scores>85 ($p<0.03$).

Association of Mental Development Scores (MDS) with parameters of thyroid function

When using the Brunet-Lezine scores at different ages, we found that children with lower language indexes at 24 months presented higher TSH concentrations and lower T3 and T4 at 30 days of life ($p<0.05$). The light damage group had lower concentrations of total T3 and T4 at all ages. Also, high Tg during the first 15 days of life was associated with a lower QT index and motor development at 24 months was negatively correlated with Tg values in the first week. Children with higher TSH during the first 30-60 days of life have lower rates in postural and motor control, oculo-motor coordination, adaptive behavior to objects and language skills ($p<0.05$).

There were significant differences in neurodevelopment rates among children in the lightweight damage group. These children had

lower T4 and T3 levels during the first 2 months of life compared to the children of the same age and pathology. The affected fields were the eye-motor coordination index and adaptive behavior to objects, partial index of global language and IQ.

There was no correlation between Apgar scores and intraventricular hemorrhage or administration of dopamine or insulin during the neonatal period.

When using Bayley test there was no significant correlation between the scores at 24 months, total, free T4 and T3. However lower mental developmental scores at 24 months was related to high TSH levels during the first week of life, corrected for gestational age ($p<0.01$).

Although advances in high-risk obstetric and neonatal care have resulted in improved survival of infants born preterm, many studies have documented the prevalence of a broad range of neurodevelopmental impairments in preterm survivors. Although some outcomes remained unchanged, the rates of low neurodevelopmental scores had improved.

Among the conditions leading to poorer health are reactive airway disease or asthma, recurrent infections and poor growth. The smallest and most immature infants have the highest risk of health problems and neurodevelopmental disabilities. Many factors influence the outcomes for infants born preterm, including gestational age at birth, weight, complications that injure the brain, variations in the clinical management of infants at various health care institutions, the family's socioeconomic condition and the mother's health, as some conditions as diabetes and hypothyroxinemia during gestation.

Although some outcomes remained unchanged, the rates of low neurodevelopmental scores had improved.

This study represents a dataset investigating postnatal iodine intake, T3 and T4, TBG and TSH serum levels in preterm infants 24-30 weeks gestation.

The key findings of the study are that iodine content in artificial formulae for infants has lower iodine content than breastmilk. Iodine intake in preterm infants is very low during the first week and lower than recommendations at least during the first month of age. There is a relationship between iodine intake and thyroid function, between outcome and thyroid function and iodine status (as independent variables).

We provide more evidence that the group of infants under 30 weeks is particularly distinct from other preterm groups. Breast milk contained more iodine than most formulae, especially those for premature babies. The daily iodine intake was far below the Recommended Dietary Allowance (RDA) of >30 μg I/kg for preterm babies. We conclude that formula-fed premature babies not taking enough volume of milk are at risk of iodine deficiency. If the mother has adequate iodine intake, breast milk is the best source of iodine for the premature infant. We concluded that low iodine intake during the first 30 days of life have a negative impact on the neurodevelopmental indexes during the first 24 months of life.

The immediate obvious conclusion regarding the interruption of the maternal supply of iodine is that care should be taken to provide the recommended minimum iodine intake, so that the external iodine supply would not be a rate-limiting factor for the synthesis of thyroid hormone. The volume of food ingested by the infant should be taken into account when assessing the iodine intake with a given formula preparation and supplements should be provided if found to be inadequate. This measure has no risk, since the margin between the recommended iodine intake and the dose required to block the thyroid gland is quite large.

Parenteral nutrition does not supply the premature neonate with enough iodine; therefore, supplements should be added if iodine intake is found to be inadequate. As many preterm infants are fed parenterally for prolonged periods with solutions shown to be low in iodine, trials have been designed to establish whether iodine supplementation of preterm infants benefits neurodevelopment , but increasing the iodine content in parenteral preparations should be considered and encouraged [34].

Even if the iodine supply is adequate, it may not be sufficient to avoid the hypothyroxinemia of premature neonates. Mimicking intra-uterine conditions by transient postnatal treatment with T4 might improve maturational events related to the hypothalamic-pituitary-thyroid system. Several groups have already performed trials to improve postnatal development of preterm neonates with postnatal T4 treatment, obtaining either inconclusive or conflicting results [35-37]. However, care should be taken that iodine supply is adequate for all newborn infants.

Conclusion

We found that iodine deficiency and low thyroid parameters during the neonatal period are independent predictors of neurodevelopmental outcomes in very low birth weight infants. Multiple factors may contribute to the causes of low neurodevelopmental scores but alterations in thyroid parameters in preterm infants and iodine deficiency play a role. Therefore it is important to keep track of those children who had thyroid parameters alterations during the neonatal period.

The overall findings in Bayley scores of our cohort at 24 months may be viewed with cautious optimism. Efforts to continue to improve outcome must include clinical trials to evaluate interventions currently in use and novel interventions. This study supports the importance of vigilant monitoring of perinatal interventions, improvements in nutrition and neurodevelopmental outcomes of ELBW infants over time.

Finally, a number of biological and environmental factors may affect the risk of adverse outcomes independent of gestational age or birth weight. To the extent that such independent risk factors have been identified, including some of those related to nutrition during the neonatal period, as iodine necessities that may ameliorate the risks due to prematurity, they are discussed. Nevertheless, researchers are far from understanding all these factors and prediction of the outcome for an individual child born preterm with any degree of certainty remains impossible.

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