IODINE AND IODOTHYRONINE CONTENT IN HUMAN NEONATE THYROID GLAND

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Abstract – A few years after the iodine content of salt in Serbia was increased from 7 to 15 mg/kg NaCl, iodine, thyroxine (T4) and triiodothyronine (T3) concentrations were measured in thyroid tissue obtained at autopsy from 21 human neonates who died within 30 days after birth. The thyroidal iodine as well as T4 and T3 content per gland increased progressively with gestational age of human neonates (r = 0.73, 0.70 and 0.67 respectively, p < 0.001). In seven newborns (gestational age 36 to 41 weeks) the mean values for total iodine, T4 and T3 per gland were 109.1 µg, 52.2 µg and 4.4 µg, respectively. The results of iodine and iodothyronine content found in neonatal thyroid gland, particularly at the end of gestation and a few days of postnatal life, indicates that the iodine supply was satisfactory.

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INTRODUCTION

In the human fetal thyroid gland accumulation of iodine starts from the 10th to 12th week of gestation (Fisher and Klein 1981). By that time the fetal thyroid has developed its characteristic histological features and became capable of synthesizing iodothyronines. At midgestation fetal thyroid gland iodine uptake and serum thyroxine concentrations begin to increase (Fisher et al. 1976; Fisher and Polk 1989; Thorpe-Beeston et al. 1992). At the same period an increase in pituitary and serum thyrotropin (TSH) occurs (Fisher et al. 1976; Fisher and Polk 1989).

The pituitary-thyroid axis matures with the development of thyroid hormone feedback inhibition of TSH production at 36 to 40 weeks of gestation in the human fetus (Fisher and Klein 1981). Immediately postpartum, remarkable changes occur in serum hormone levels of this axis, since this is a period of intense adjustment to the extra uterine environment. During the first few hours of extra-uterine life there is a sudden increase of TSH in the circulation, followed by a rapid rise in iodothyronine concentration. The initial increase of thyroid hormones in the circulation is mainly due to increased secretion by the thyroid gland under the influence of TSH and some other factors (such as catecholamines). After this surge of TSH and thyroid hormones, their concentrations decrease to reach levels characteristic for adults by the age of one month (Fisher et al. 1976; Roti 1988; Fisher and Polk 1989). Although the function of the pituitary-thyroid axis of the human neonate in the early period after birth has been extensively investigated (Czernichow et al. 1971; Abuid et al. 1973; Fisher and Klein 1981), there are few data about thyroid hormone synthesis, i.e. iodine and iodothyronine content in neonatal thyroid gland (Etting 1977; Costa et al. 1986; Savin et al. 1996; Van den Hove et al. 1999). This study was focused on the iodine, as well as iodothyronine content in thyroid tissue of preterm and term neonates, particularly in relation to their gestational age and survival.

MATERIAL AND METHODS

Thyroid glands were collected from the Department of Pathology, Clinic of Gynaecology and Obstetrics, Belgrade, Yugoslavia. All human thyroids were collected according to the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration of 1975, as revised in 1983. Newborns were classified into two groups according to their gestational age: 14 preterm infants (from 25 to 35 gestational weeks) and seven neonates born close to – term and at term (36 to 41 gestational weeks). All neonates died during the first month after birth and none was exposed to iodine overload (including iodinated contrast media and iodinated disinfectants on the umbilical cord) before death.
All neonates were weighed and their age was estimated from the maternal menstrual history and measurement of fetal size. Post mortem examination was performed for each case. Mortality in the preterm and term neonates was due to cardiovascular abnormalities (N = 2), respiratory distress syndrome (N = 10), pulmonary diseases (N = 5), intracranial haemorrhage (N = 1), diaphragma hernia (N = 1) or abruption of placenta (N = 2).

After the gland had been removed and weighed, thyroid tissue was minced with scissors and then homogenized in phosphate buffered saline (PBS, pH 7.4, 1 mL per 100 mg wet tissue). The homogenate was successively centrifuged to remove subcellular fractions. The procedure for the preparation of thyroid extracts was described in detail by Sinadinović et al. (1986). The 105 000 x g supernatant contained soluble thyroid proteins and was used for further investigation. Iodotyrosines were determined by radioimmunoassay (T3 – RIA and T4 – RIA, INEP) after enzymatic hydrolysis of the supernatant with pronase (Chopra et al. 1973). Iodine content in extracts was measured by a standard method based on the oxidation of arsenic 3+ ions by cerium 4+ ions in the presence of iodide as a catalyst (Lauber 1975).

Data are given as means ± standard deviation (SD). The differences in mean values between two groups were analysed with the Mann–Whitney test. Association between variables was expressed as the correlation coefficient and it was considered statistically significant at p < 0.05.

RESULTS

This study comprised 21 thyroid glands of human neonates of gestational age from 25 to 41 weeks. The mean thyroid weight of 14 preterm neonates was 0.64 ± 0.23 g, while for 7 close-to-term and term infants 1.16 ± 0.54 g. The body weights of the newborns increased proportionally with respect to gestational age. Thus, the mean body weight obtained for the preterm group was 1.65 ± 0.62 kg and for the group of older neonates 2.82 ± 0.86 kg. During the investigated period of development the ratio of thyroid gland weight to body weight decreased slightly but not significantly (Fig 1), individual values varied considerably from 0.021 to 0.081%, with an overall average of 0.043%.

Fig 1. The relationship between thyroid gland weight ratio to body weight (%) and gestational age at birth of neonates between 25 and 41 weeks of development. Each point represents the value for one neonate. The negative correlation was not statistically significant (p > 0.05).

The mean values for iodine, T4 and T3 concentrations were not significantly different between the two groups of neonates (Fig. 2). In the first group, iodine content was 72.5 ± 35.5 µg/g, T4 was 39.5 ± 22.7 µg/g and T3 3.1 ± 1.5 µg/g. In the second group the corresponding values were 96.7 ± 41.5, 46.3 ± 22.4 and 4.0 ± 1.8, respectively (all values in µg/g wet weight). The highest value found for iodine was 160 µg/g and for T4 87.4 µg/g, in a neonate of gestational age 37 weeks, who survived for further 26 days (Fig. 2). Taking into account all data there was a statistically significant linear correlation between gestational age at birth and iodine concentration in thyroid tissue of human neonates (regression line: y = 4.843x + 82.026; r = 0.51; N = 21; p < 0.05). The correlation was even closer when gestational age and survival period were considered (regression line: y = 4.586x + 76.913; r = 0.56; N = 21; p < 0.01, Fig. 2). Significant correlations were also observed between life duration and T4 concentration (regression line: y = 2.150x + 32.113; r = 0.45; N = 21; p < 0.05), as well as between life duration and T3 concentration (regression line: y = 0.157x - 1.9767; r = 0.44; N = 21, p < 0.05).

The relation between thyroid tissue iodine concentration and thyroid hormone ratio (T4/T3) is presented in Fig. 3. There was no increase in this ratio with increased iodine content of the gland (p > 0.05). In addition, no marked systematic variation with duration of life was seen. The T4/T3 ratio ranged from 7.0 to 18.0, with a mean value of 12 ± 3.
Fig. 2. Thyroidal iodine, thyroxine and triiodothyronine concentrations (µg/g wet thyroid weight) of newborn infants classified according to their gestational age into two groups. Preterm neonates were aged 25 to 35 gestational weeks. Close to term and term newborns were aged 36-41 gestational weeks. Full symbols refer to preterms and empty symbols refer to closeto-term and term neonates. No significant differences between the groups were seen. Associations between life duration (gestational age and survival) and iodine, thyroxine and triiodothyronine concentrations were determined by linear correlation analysis for the whole group of neonates \( N = 21 \) and were statistically significant \( (p < 0.05) \).

Fig. 3. The relationship between thyroid tissue \( T_4/T_3 \) ratio and thyroid iodine concentration in human neonates. Full symbols refer to preterms and empty symbols refer to closeto-term and term neonates. The groups are described in the legend to Fig. 2. Positive correlation was not statistically significant.

Total thyroidal iodine, as well as \( T_4 \) and \( T_3 \) content increased progressively with gestational age of human neonates \((r = 0.73, 0.70 \) and 0.67, respectively; \( P < 0.001) \). The mean values for total iodine, \( T_4 \) and \( T_3 \) in thyroids of preterm infants were \( 46.4 \pm 28.1 \) µg, \( 24.4 \pm 17.4 \) µg and \( 2.1 \pm 1.5 \) µg, respectively and they were significantly lower than the corresponding values for the close-to-term and full term glands \((109.1 \pm 54.6 \) µg, \( 52.2 \pm 27.5 \) µg, \( 4.4 \pm 2.3 \) µg, respectively).

**DISCUSSION**

**Thyroid weight ratio to body weight**

Thyroid gland weight to body weight ratio has been reported to remain constant from the 6th month of gestational age onwards at a mean value of 0.046 % of body weight (Shepard et al. 1964). Costa et al. (1986) found the value to be 0.063 \( \pm 0.02 \) % for 28 preterm Italian neonates of gestational age 22-34 weeks. In the present study thyroid gland weight expressed as a percentage of body weight remained constant between weeks 25 and 41 of gestation. The mean value was 0.043 % which is close to the aforementioned values, as well as that calculated from the data of Ettling and Laroche (1975). In Poland, where iodine deficiency could still be found (Delange 1996), relative thyroid gland weight was much higher (Bocian-Sobkowska et al. 1997).
Thyroid iodine and iodothyronine concentration

The average iodine and thyroxine concentrations of neonatal thyroid glands in Belgrade were somewhat higher than the levels obtained in a non-goiter region in Italy (Costa et al. 1986). Moreover, these results for thyroxine and triodothyronine concentration are much higher than those obtained previously for thyroid glands of newborns from Priština, Yugoslavia (Savin et al. 1996). This earlier study was undertaken with thyroid glands collected during a period of negligence concerning iodination and salt storage (Sinadinović et al. 1993), as well as irregularities in the salt market. Tissue iodine was not determined. In the meantime, the prescribed iodine content of salt in Serbia has been doubled (Sinadinović and Han 1995) and from that time has been considered to satisfy requirements. Direct support for this assumption was derived from the recent study of urinary iodine excretion and thyroid volume in schoolchildren in Serbia (Simić et al. 2001).

Several investigators have shown that thyroid iodine concentration increases with postnatal survival time (Etling 1977; Van den Hove et al. 1999). Our study provides some indication of a correlation between both iodine and iodothyronine concentration in thyroid gland and life duration of the human neonate, i.e. gestational age and survival period. A slightly lower iodine content in preterm neonates may be attributed to their nutritional problems. Thus, preterm neonates have a higher loss of iodine in urine, which may lead to depletion of their intrathyroidal iodine stores during early postnatal life, particularly in iodine poor areas (Delange et al. 1983). Connecting the previous data about limited iodine and iodothyronine stores in the thyroid gland of preterm neonates to the immature hypothalamo–pituitary control of the fetal thyroid gland, immaturity of the thyroid gland itself and increased tissue utilization of thyroxine (La Franchi 1999) may explain why extraterine adaptation is often more compromised in preterm neonates.

According to our results the T₄/T₃ ratio does not change with gestational age, which is in agreement with the data of Fisher et al. (1973) who observed this ratio to remain constant from the 13th week onwards. The mean value of the T₄/T₃ ratio found in this work is comparable to the data obtained for adults, namely 17.9 (Reinwein et al. 1981) and 11 (Reed–Larsen 1975) and for preterm infants 17 (Costa et al. 1986).

Iodine and iodothyronine content per gland

Previous measurements made in neonates (Etling, 1977; Delange et al. 1985; Van den Hove et al. 1999) showed that total thyroidal iodine and iodothyronine content increased with duration of life, i.e. with glandular weight. The mean total thyroid iodine in close–to–term and term Belgrade neonates was slightly higher than that reported by Delange and Ermans (1996) for term neonates in Brussels, an area of borderline iodine intake. More recent investigations of van den Hove et al. (1999) additionally suggest that the reserves of T₄ in the thyroid glands of premature newborns from Brussels were low and sufficient for less than one postnatal day. Fisher et al. (1973) examined 4 fetuses of 20, 20, 26 and 31 weeks in the U.S.A. and found that the mean value for total T₄ in thyroid tissue was about 3.8 μg and for T₃ 0.53 μg per gland. Procedures for hydrolysis of thyroid tissue and measurement of iodothyronines in the aforementioned study were similar to those employed in this work. Values for total T₄ content found in our experiment for the corresponding gestational age (seven preterms of gestational age from 25 to 31 weeks) ranged from 4.1 to 38.9 μg (mean value 16.4 μg). In the same glands the mean value for total thyroid T₃ was about 1.5 μg. Thus, our results for iodothyronine content were within the range or slightly higher than the values obtained by Fisher et al. (1973).

To conclude, our data for iodine and iodothyronine content in the investigated neonatal thyroid glands, particularly at the end of gestation and a few days of postnatal life, indicate that the iodine supply was satisfactory and coincides well with the recent report of Simić et al. (2001) about iodine status of school children in central Serbia.

REFERENCES


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La Franchi, S. (1999). Thyroid function in the premature infant. Thyroid 9, 71–78.


Неколико година након што је садржај Јода у кухињској соли повећан са 7 на 15 mg/kg NaCl, концентрација Јода, тироксина (Т₄) и тријодтиронина (Т₃) мерена је у тироидном ткаву добијеном након аутоопције 21 новорођенчата, који су умрли током првог месеца. Укупан садржај Јода, тироксина и тријодтиронина у јегитастој жлезди растао је упоредо са гестацијском старошћу новорођенчади, а одговарајући коефицијенти корелације за ове промене су 0,73; 0,70; и 0,67 (p<0,001). Код седам новорођенчади (гестацијске старости између 36 и 41 недеље) просечне вредности концентрације Јода су 109.1 μg, Т₄ 52.2 μg и Т₃ 4.4 μg. Садржај Јода и јодотиронина у тироидној жлезди новорођенчади, нарочито крајем гестације и након неколико дана живота, указује да је снабдевање једном било задовољавајуће.