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Evaluation of the effect of maternal iodine status on recall frequency in newborn TSH screening

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Abstract

Objective: Pregnant and lactating women are particularly at higher risk of iodine deficiency due to their increased iodine requirements. Iodine is necessary for normal growth and brain development. In regions with moderate iodine deficiency, such as Turkey, the fate of newborn babies is a critical issue.This study evaluated the relationship between maternal iodine deficiency and the frequency of recall due to high TSH value in newborn screening programs.

Methods: 78 mothers who volunteered for the research were included in the study with their newborn babies. Thyroid function tests were examined in the blood serum of newborns with high heel blood TSH value (5.5-20mIU/L) who were referred to the pediatric endocrine with the suspicion of congenital hypothyroidism Urinary iodine levels of healthy mothers without any thyroid disease and iodine exposure were evaluated.

Results: The median urinary iodine in mothers was 56.04 μg/l. Only 8 (10.2%) of the recalled newborns had subclinical hypothyroidism and recovered at the follow-up 1 week later, while all the rest had normal thyroid functions. In addition, there was a weak negative correlation between maternal age, the number of children, and urinary iodine levels (respectively, r=0.35,r= 0.33; p=0.001,p=0.003).

Conclusion: Only 9%(7 people) of the mothers participating in the study had adequate urinary iodine excretion and almost half (38 people) of the mothers (48.7%) had severe urinary iodine deficiency. Low maternal iodine values are effective in the prolonging transient TSH elevation in newborns, and iodine supplementation to mothers during pregnancy may reduce recall rates of newborn TSH screening.

Keywords: Nutritional supplements, iodine, neonatal screening, thyroid stimulating hormone

Introduction

Iodine is required from the early stages of the embryo for the adequate production of thyroid hormones, which are necessary for normal growth and brain development.[1] Iodine deficiency effects can occur at different times throughout life, although controversial, there is some indication that maternal iodine deficiency, even mild, during pregnancy may reduce intelligence and cognitive development in offspring.[2-4]

Iodine deficiency is one of the major factors in the increased recall rate (due to elevated TSH) and the increased incidence of transient congenital hypothyroidism. Babies born in iodine-deficient regions tend to have adaptively elevated thyroid-stimulating hormone (TSH) concentrations to keep serum thyroxine (FT4) in the normal or low-normal range.[5]

Although iodization of salts in Turkey has been carried out by state regulation since 1998, moderate iodine deficiency can be seen especially in rural areas of Turkey. In this study, we aimed to evaluate urinary iodine levels in mothers with newborn babies who were found to have elevated TSH in heel blood screening and were referred to the Pediatric Endocrinology outpatient clinic with the suspicion of congenital hypothyroidism.

Methods

78 mothers who agreed to participate in the study were included in this cross-sectional study with their newborn

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babies. The average age of the mothers was 26.94 years (15-39). All mothers were apparently healthy women, and none had a history of past or current thyroid disease, recent exposure to iodine, intake of goitrogenic drugs, and thyroid hormones. These mothers who delivered vaginally or by cesarean section (44 and 34 person, respectively) did not experience any complications during pregnancy and delivery. Their parities ranged from 1 to 6 (mean 2.60).

According to the screening program of the Ministry of Health of the Republic of Turkey, the heel blood is checked for the second time in babies with a TSH elevated value (between 5.5 and 20 mIU/L) in the first week. In case of persistent elevation, they are referred to an advanced center to study serum thyroid functions (Figure 1). All babies were born at term and all of them were screened 2 times for heel blood relevant to this program. They were referred to Pediatric Endocrinology because of the elevated TSH (5.5-20 mIU/L) in the screening. None of the 78 newborns had a goiter or clinical manifestations of thyroid insufficiency. TSH, free T4, free T3 and thyroglobulin values of all babies who applied to the outpatient clinic were measured from peripheral blood samples. Urine iodine concentration was measured in spot urine samples taken from all mothers. Urine iodine levels were measured by inductively coupled plasma mass spectrometry method (ICP-MS). Urine iodine results are expressed as µg/l. Classification of the severity of maternal iodine deficiency was made according to the criteria recommended by WHO/UNICEF/ICCIDD based on urinary iodine excretion (UIE) [6] values; therefore, urinary iodine values below 25 are classified as severe deficiency, between 25 and 49 as moderate deficiency, between 50 and 99 as mild deficiency and above 100 as adequate. The approval of the study was obtained from the ethics committee of Gaziantep University Faculty of Medicine (Number:2021/114).

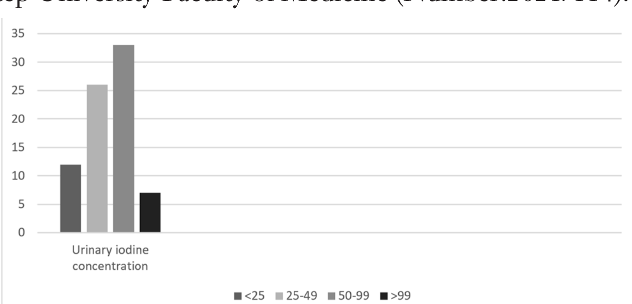

Figure 1. Frequency distribution of urinary iodine concentrations (µg/l) in mothers

Statistical analysis

The statistical analyses were performed using SPSS, version 22 (IBM SPSS Statistics for Windows, Armonk, NY; IBM Corp., Released 2013). First, a Kolmogorov-Smirnov test was used to determine which variables should be included in the data analysis and whether the data for the variables were normally distributed, but the data were not normally distributed. Therefore, non-parametric tests were used. The Mann-Whitney U test was used to compare continuous variables across the groups. The relationship between continuous variables was examined with Spearman Correlation Coefficient. The median (Q1 (1st quartile)-Q3 (3rd quartile)), mean ± standard deviation, frequency and percentage were reported as descriptive statistics correlation coefficient. The statistical significance level was set to $p < 0.05$.

Results

78 mothers and their babies who agreed to participate were included in the study. The mean age of the mothers was 26.9 ± 5.19 years. Parities of mothers were between 1 and 6 (mean 2.60). All infants were screened twice for heel blood and were referred to pediatric endocrinology for elevated TSH (5.5-20 mIU/L) results. The mean body weight of the newborns was 4305 ± 514 g and the mean body SDS values were 0.15 ± 0.87. 39 babies (50%) were girls. 44 babies (56.4%) were born by normal vaginal delivery, and 34 (43.6%) by cesarean section.All studies were performed on a mean postnatal 29th ±5 day at admission. Of the newborns, 57 (73.1%) were fed only with breast milk, 19 (24.4%) with both breast milk and formula, and 2 (2.6%) with only formula. No relationship was found between nutritional status and maternal iodine level. The median heel blood TSH values of babies are 15.80 ± 10.3 mU/l. The median serum concentrations (and ranges) of neonatal TSH, Tg, FT3 and FT4 were 3.18 ± 2.13 mU/l, 157.4 ± 132.06 µg/l, 4.28 ± 0.60 pg/ml and 1.23 (0.80–1.70) ng/dl respectively (Table 1). Thyroglobulin results could not be obtained in 7 patients due to missing sampling errors. The frequency distribution of urinary iodine concentrations in mothers is shown in Figure 2. The median urinary iodine value of the mothers was 56.04 µg/l, with 91% (71person) of the values below 100 µg/l, 48.7% (38 person) below 50 µg/l and 15.4% (12 person) below 25 µg/l. Only 7 mothers (9%) had urinary iodine above 100 µg /l. There was a statistically significant and weak negative correlation between maternal age and urinary iodine level ($r=-0.359$, $p=0.001$). In addition, there was a statistically significant and weak negative correlation between the number of children and urinary iodine level ($r=-0.333$, $p=0.003$). There was no significant relations-

hip between urinary iodine level and any other parameter. The correlation analyzes between the variables are given in Table 2. In addition, although TSH values of 8 babies were >5mU/l, FT4 values were within the normal range. The control thyroid function values, which were checked one week later, were normal in all of these patients, who were followed up without medication and were given their mothers a recommendation for the enrichment of iodine intake sources. 57 of the infants (73.07%) were receiving only breast milk, and 21 (26.93%) were receiving formula together with breast milk. There was no significant relationship between diet and any parameter.

Table 1. Laboratory findings of newborns

Parameter	Neonatas	Reference range
	mean±SD (min-max)	
TSH (mU/l)	3.18 ±2.13 (0.4-7.1)	(0.35-5.5)
Screening bloodTSH	15.8 ±12.62 (5.5-61.2)	(<5)
FT4 (ng/dl)	1.23 ±0.19 (0.9-1.7)	(0.89-1.76)
FT3 (pg/ml)	4.28 ±0.60 (2.3-5.4)	(3.00-4.7)
Tg (ng/ml) *	132 ± 157 (9.2-500)	(3.30-77)

* Thyroglobulin results could not be obtained in 7 patients due to missing sampling errors.

Table 2. Correlation between Variables

		2	3	4	5	6	7	8	9	10	11
1	**Urin iodin**	-0,141	-0,153	-0,016	0,013	-,333**	0,018	-0,053	-0,034	-0,147	-,359**
2	**Birth weight**	1	-0,161	,546**	,525**	0,205	-0,089	0,028	0,03	0,048	0,16
3	**Heel blood TSH**		1	-,262*	-,337**	-0,097	0,215	0,083	0,096	,417**	-0,1
4	**Weight**			1	,810**	0,055	-0,117	-0,052	-0,011	-0,177	0,034
5	**Weight SD**				1	0,157	-,254*	-0,062	-0,022	-0,176	0,051
6	**Child's rank in the family**					1	-0,15	0,144	0,084	0,044	,642**
7	**TSH**						1	-0,142	0,139	,248*	0,16
8	**Free T4**							1	,305**	0,082	0,107
9	**Free T3**								1	,329**	0,192
10	**Thyroglobulin**									1	0,019
11	**Maternal Age**										1

Notes: TSH: thyroid stimulating hormone, SD: standard deviation, ** p<0.01, * p<0.05

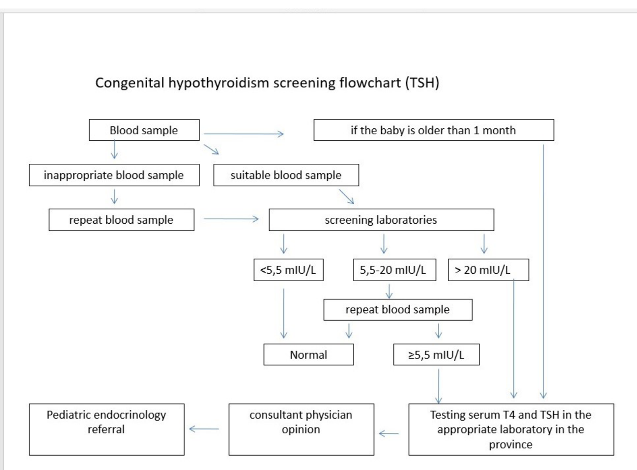

Figure 2. Congenital hypothyroidism screening flowchart (TSH) according to Turkish Ministry of Health

Discussion

Iodine is one of the micronutrients. It is found in trace amounts in the human body and its most important role is in the synthesis of thyroid hormones. Also, newborns and infants are much more severely affected by iodine deficiencies than adults and are more likely to develop overt cases of hypothyroidism, cretenism and goiter.[7,8] The damage increases with the degree of deficiency, with clear endemic cretinism as the most severe outcome. All degrees of iodine deficiency are determined by median urinary iodine in µg/l (mild 50-99, moderate 20-49, severe<25) . Maternal hypothyroxinemia in early pregnancy is an important factor in the development of neurological damage in cretinism. Iodine deficiency (ID) causes 10-15 loss of intellectual quotient points globally at the population level and is the world's single largest cause of preventable brain damage and mental retardation.[9]

In light of conflicting data, the European and American Thyroid Societies recommend iodine supplementation (250 µg/day) during pregnancy, while WHO does not recommend it for women living in countries with effective and sustained iodized salt programs. In other words, it is still unclear whether iodine supplementation during pregnancy is warranted in areas where iodized salt is available. [12]

The salt iodization program was initiated by the Turkish Ministry of Health in 1998 and was revised in 2010 to indicate that the recommended iodine concentration should be 25-45 mg/kg potassium iodate. Although salt iodization is now legaly mandated, [10] which helps to greatly reduce iodine deficiency, [11] ID remains a major public health problem, particularly in rural areas of Turkey. In our study, we found iodine deficiency in more than half of the mothers with an average urinary iodine level of 56.04 µg/l.

According to figures from previous epidemiological studies, Turkey has long been known as a country with mild to moderate iodine deficiency. [13-14] The prevalence of total goiter in Turkey was 30.5% and the prevalence of apparent goiter was as high as 6.7%. In addition, it has been shown that the prevalence of goiter does not fall below 2% in any region after salt iodization, and can reach up to 22.5% in some regions. [15,16] In our study, we found a high rate of iodine deficiency among mothers who had just given birth, living in the city center rather than in rural areas. For this reason, iodine support should be kept in mind during the phases of increased need, especially for women during pregnancy and lactation.

In contrast to the situation in mothers (despite iodine deficiency, there may be no significant thyroid function changes), the changes in thyroid function that occur in newborns with ID are much more pronounced, including particularly high serum TSH and Tg concentrations. This particular hypersensitivity of the newborn to ID is due to small iodine stores in the neonatal thyroid, which has a very rapid cycle. [17] Therefore, it has been suggested to use neonatal thyroid screening programs measuring primary TSH as the primary monitoring tool in evaluating the degree of ID in populations and the effectiveness of iodine supplementation programs. [6,17] UI excretion is a good predictor of final dietary iodine intake, as over 90% of iodine absorbed by the body eventually appears in the urine. [18] In our study, we found low iodine levels in the urine samples of mothers of newborns with resistant TSH elevation in the postnatal 1st month.

Likewise, the WHO has reported that the distribution of neonatal TSH concentration along with the median urinary iodine of school-aged children are sensitive indicators of population iodine. [19] Median urinary iodine <100 µg/l in school-aged children and newborn TSH > 5 mU/L in whole blood in more than 3% of newborns indicate iodine deficiency. On a population basis, especially in countries with moderate to severe iodine deficiency, there is a negative relationship between urinary iodine concentration and neonatal TSH values, but in countries with mild to borderline ID, low urinary iodine is not accompanied by a change in blood TSH concentration. [20] The findings of this study showed that maternal iodine deficiency may be associated with permanent but transient TSH elevation in the newborn, especially in the first month, supporting our study.

Thyroglobulin is the most abundant protein in the thyroid, which provides the matrix for thyroid hormone synthesis. It is normally secreted in small amounts from the thyroid or leaks spontaneously into the circulation. Much larger amounts are released when the thyroid is hyperplastic or injured. Thyroid hyperplasia of iodine deficiency is associated with regularly increased serum Tg levels. In this environment, it reflects iodine nutrition for months or years. In population studies, thyroglobulin is a sensitive marker of iodine deficiency and is sometimes considered more sensitive than TSH. [21,22] In our study, the mean thyroglobulin level of newborns was increased by 132 ng/ml. This result may be a clue that iodine deficiency in newborns manifests itself with high TSH in the screening program.

High recall rates in newborn screening may be due to many factors, such as different screening strategies (use of T4 or TSH or both), different laboratory techniques, sample collection site, iodine status, different recall criteria, and human error; [23] among these factors, iodine deficiency seems to be more of a concern especially in Turkey. In our study, urinary iodine levels were measured in mothers of infants who were referred to pediatric endocrinology with a pre-diagnosis of congenital hypothyroidism with neonatal heel-resistant high TSH (5.5-20 mIU/L) value. it was below 100 µg/l in 91% of the mothers, which was much lower than the recommended values for the breastfeeding period (100-200 µg/l). Although newborns whose mothers had urine iodine levels were referred to the hospital for further evaluation due to persistent heel blood TSH elevation in the first month, serum TSH levels fell below 5mU/l and were within normal limits.

Pregnant and lactating women and neonates are populations in which ID effects are severely seen due to the impact of maternal, fetal and neonatal hypothyroxinemia on brain development. [17,18] Therefore, any program to correct iodine deficiency in a population should pay special attention to these particular groups. However, there are currently no definitive recommendations currently available on the agreed UI concentration indicating optimal iodine nutrition in these groups. [24]

Conclusion

In conclusion, this regional cross-sectional study, conducted in a region of Turkey that was affected by severe iodine deficiency in the past, shows that despite the implementation of a mandatory salt iodization program, moderate to almost severe iodine deficiency persists in Southeastern Anatolia and that thyroid function is impaired especially in pregnant women, lactation mothers, and newborns.

According to this study, we recommend iodine supplementation to pregnant women, so that it will reduce the frequency of transient TSH elevation in newborn babies and reduce recalls due to heel blood screening.

There is a need for studies with larger series that can guide the necessity of iodine supplementation for newborn and pregnancy period.

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