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ORIGINAL CONTRIBUTION

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Iodine status remains critical in mother and infant in Central Anatolia (Kayseri) of Turkey

Summary *Background* Severe iodine deficiency disorders have been eradicated in many parts of the world, but milder forms still exist and may escape detection. Turkey has long been known to be a mild to moderate iodine deficiency area. *Aim of the study* The aim of this study was to assess the iodine nutritional status and the thyroid function of pregnant women and their neonates in the region of Kayseri (central Anatolia of Turkey) that appeared to be iodine deficient in previous studies performed before the introduction of mandatory salt iodization. *Methods* A cross-sectional voluntary screening study was performed in the Maternity Unit of a university hospital. A total of 70 mothers and their healthy full-term neonates were included in this study. Urinary iodine concentration was estimated in spot urine samples obtained from mothers and their neonates on day 5. All the neonates were breastfed. The iodine content was determined in the breast milk of all mothers on day 5. Serum concentrations of TSH, thyroglobulin (Tg), free triiodothyronine (FT3) and free thyroxine (FT4) were investigated in the cord serum of neonates and compared to those of mothers immediately after parturition *Results* The median urinary iodine on day 5 in mothers and their babies were 30.20 and 23.80 µg/l, respectively. These figures are much lower than normal for these age groups (150–200 µg/l). The median iodine content of breast-milk was 73 µg/l. It is again much lower than in iodine sufficient areas, indicating that the status of iodine nutrition of pregnant and lactating women is clearly insufficient. The median concentrations (and ranges) of neonatal TSH, Tg, FT3 and FT4 were 7.44 mU/l, 71.62 ng/ml, 1.30 pg/ml and 1.34 ng/dl respectively. The corresponding levels for the mothers during labor were 2.19 mU/l, 25.65 ng/ml, 1.31 pg/ml and 1.23 ng/dl respectively. The median neonatal serum concentrations of TSH and Tg were significantly higher than the corresponding maternal levels ($P < 0.0001$, $P < 0.0001$, respectively) and 27.1 % of the neonates had serum TSH concentrations above 10 mU/l and 57.1 % had cord blood serum Tg concentrations above 54 ng/ml. None of the mothers showed TSH concentrations above 5 mU/l and 41.4 % had serum Tg concentrations above 30 ng/ml. *Conclusion* Iodine deficiency with low urinary iodine excretion and high serum Tg and TSH concentrations were recognized among pregnant women and their babies in Kayseri in spite of the program of salt iodization. National measures are urgently required for improving the correction of iodine deficiency in Turkey. This includes regular supplementation with iodine, starting at preconception or in early pregnancy and continuing during the period of nursing in this region.

Key words iodine deficiency – urinary iodine – breast-milk iodine – thyroid function – neonates – pregnancy

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Introduction

Children born in iodine deficient areas are at risk of neurological disorders and mental retardation because of the combined effects of maternal, fetal and neonatal hypothyroxinaemia [1]. The reasons are that iodine is required for the synthesis of thyroid hormones and that thyroid hormones, in turn, act by regulating the metabolic pattern of most cells of the organism. They also play a determining part in the process of early growth and development of most organs, especially of the brain, which occurs in humans during fetal and early postnatal life [2–4]. Consequently, iodine deficiency, if severe enough to affect thyroid hormone synthesis during this critical period, will result in hypothyroidism and brain damage. The clinical consequence will be mental retardation. Iodine deficiency is the leading cause of preventable mental retardation in children [5]. In 2001 alone, some 50 million children were born without any preventive measures having been taken against IDD during pregnancy [6]. The iodine status of breastfed infants is largely dependent upon the iodine content of breast milk. In marginally iodine-deficient areas, the administration of iodine is recommended during pregnancy and lactation.

The recommended dietary allowances of iodine recently proposed by the World Health Organization (WHO), the United Nations Children's Fund (UNICEF) and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) are 90 µg/day from 0 to 6 years, 120 µg/day from 7 to 10 years, 100 µg/day in adolescents and adults and 200–300 µg/day during pregnancy and lactation [7].

In 1992, most European countries, with the exceptions of Switzerland, Austria, Great Britain, and most Scandinavian countries, were still affected by mild to moderate degrees of iodine deficiency [8]. Turkey has long been known as a mild to moderate iodine deficiency area according to the figures obtained from previous epidemiological studies [9–14]. Recently, the Ministry of Health started to work on a national salt iodization program to improve the iodine intake nationwide.

The objectives of the present study were 1) to evaluate the status of iodine nutrition of Turkish mothers and their full term neonates by measuring their concentrations of urinary iodine, 2) to measure the iodine content of the breast-milk offered to these neonates, 3) to compare these results to those obtained for the same variables in iodine replete areas in the world and 4) to determine the influence of this deficiency on the thyroid function of the mother and neonate.

Subjects and methods

Subjects

We enrolled 70 pregnant women whose ages ranged from 18 to 37 years (mean 25.51 years) and their full term neonates into a cross sectional voluntary screening study. All the mothers were apparently healthy women and none of them gave any history of past or present thyroid disease, recent exposure to iodine, intake of goitrogenic drugs and thyroid hormones. All women lived in the city of Kayseri or the surrounding areas, a region known to present moderate to severe iodine deficiency. The women were admitted for delivery at Erciyes University maternity unit. All women delivered spontaneously and none experienced complications during pregnancy or delivery. Their parity ranged from 1 to 5 (mean 2.25). They gave birth to apparently healthy singleton full term babies. None of the 70 neonates had goiter or clinical signs of thyroid failure. The ethical committee of the Faculty of Medicine approved the protocol.

Methods

We discharged all the mothers and infants after a hospital stay of 24 hours and called them back on the 5^{th} day after delivery. The estimation of urinary iodine concentration was performed in spot urine samples obtained from all mothers and their newborns on the 5^{th} day after delivery. The iodine content of breast milk was also determined in all mothers on day 5. Milk samples were obtained by manual expression into de-iodinated glass vials. Sampling was done at the mid-morning feed from both breasts. Urine and milk specimens were stored at –70 °C until required for analysis. Iodine was determined by using reversed-phase high-performance liquid chromatography (HPLC) [15, 16]. The results were expressed in µg/l. The intra- and interassay coefficients of variation for determination of milk iodine concentrations and urinary iodine excretion (UIE) were $< 10\%$. Classification of the severity of iodine deficiency in the mothers was performed according to the criteria proposed by WHO/UNICEF/ICCIDD based on urinary iodine excretion (UIE) values [17]; thus, urinary iodine values less than 25 are severe, between 25 and 49 moderate, between 50 and 99 mild, and higher than 100 adequate [17].

The women provided approximately 10 ml venous blood just before delivery. A doctor or a trained midwife obtained cord blood samples (10 ml) during delivery. The blood samples were allowed to coagulate at room temperature before separation of the serum by centrifugation. The serum samples were frozen within 1 h of sampling and then kept frozen at –70 °C until analysis.

FT3 and FT4 were measured by radioimmunoassay

(Amersham, UK). TSH (Amersham, UK) and Tg (CIS bio international, France) were determined by using a sensitive immunoradiometric assay. For FT3, the reference range in Turkish adult nonpregnant subjects is 2.30–6.60 pg/ml, the sensitivity was 0.456 pg/ml and intra- and interassay coefficients of variation were 4 % and 6.4 %, respectively, and, for FT4, 0.8–2.3 ng/dl, the sensitivity was 0.046 ng/dl and intra- and interassay coefficients of variation were 6.5 % and 7.5 %, respectively. These criteria were chosen from the reference range given by the laboratory for daily use. For TSH, the sensitivity was 0.04 mU/L and intra- and interassay coefficients of variation were 1.6 % and 4.3 %, respectively. For Tg, the sensitivity was 0.5 ng/ml and intra- and interassay coefficients of variation were 3.3 % and 6.9 %, respectively.

In mothers, biochemical criteria of excessive thyroid stimulation was defined by a serum thyroglobulin greater than 30 ng/ml [18, 19]. Cord blood normal thyroglobulin level is 2–54 ng/ml [20].

In the absence of iodine deficiency, the frequency of neonatal TSH above 5 mU/l whole blood (or 10 mU/l serum) is less than 3 %. A frequency of 3 %–19.9 % indicates mild IDD. Frequencies of 20 %–39.9 % and above 40 % indicate moderate and severe IDD, respectively [17, 21, 22].

Statistical analysis

All data processing was done with the Statistical Package for Social Sciences SPSS 10.0 software for Windows. Commonly used statistical methods (means, medians, proportions) were applied to analyze the data. The data were not found to be normally distributed. The level of significance in all statistical tests was set at $p \leq 0.05$. The Mann-Whitney U-test and Pearson's correlation were used for independent variables.

Results

Urinary iodine concentrations in mothers

The frequency distribution of urinary iodine concentrations in mothers is shown in Fig. 1. The median value on the 5th day after delivery was 30.20 µg/l with 90 % of the values below 100 µg/l, 65.7 % below 50 µg/l, and 41.4 % below 25 µg/l, respectively.

Urinary iodine in newborns

The frequency distribution of urinary iodine concentrations in the full term neonates is shown in Fig. 2. The median value on day 5 was 23.8 µg/l with 100 % of the values below 100 µg/l, 82.9 % below 50 µg/l, and 51.4 % below 25 µg/l, respectively. There was a weak but significant correlation between the newborn and maternal urinary iodine levels ($p < 0.05$, r: 0,24).

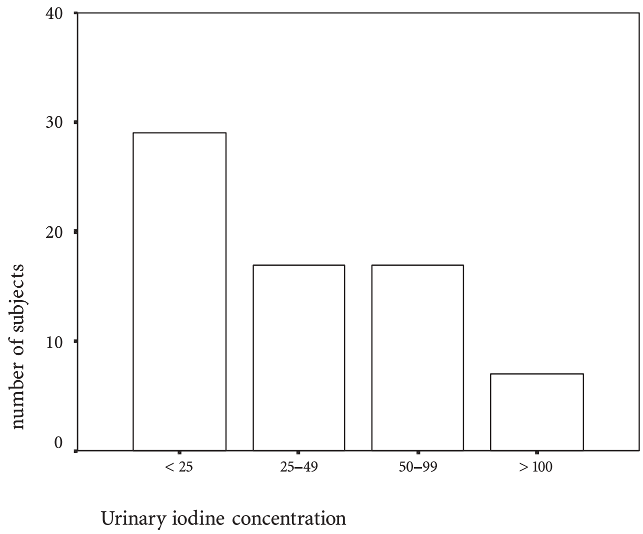

Fig. 1 Frequency distribution of urinary iodine concentrations (µg/l) in mothers on the 5th day of delivery

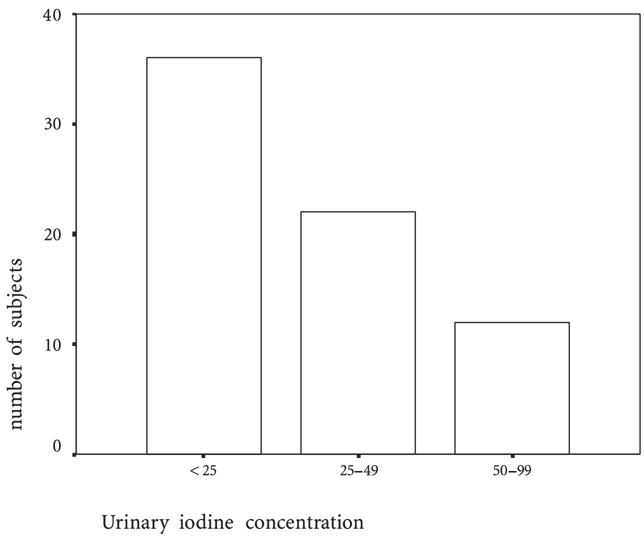

Fig. 2 Frequency distribution of urinary iodine concentrations (µg/l) in full term neonates on the 5th day of life

Iodine content of breast-milk

The frequency distribution of breast-milk iodine is shown in Fig. 3. The median value was 73 µg/l (range: 9.50–355.60) µg/l with 72.9 % for the values below 100 µg/l, 37.1 % below 50 µg/l and 5.7 % below 25 µg/l. We did not find any correlation of the content of breast milk levels to urinary excretion in newborns.

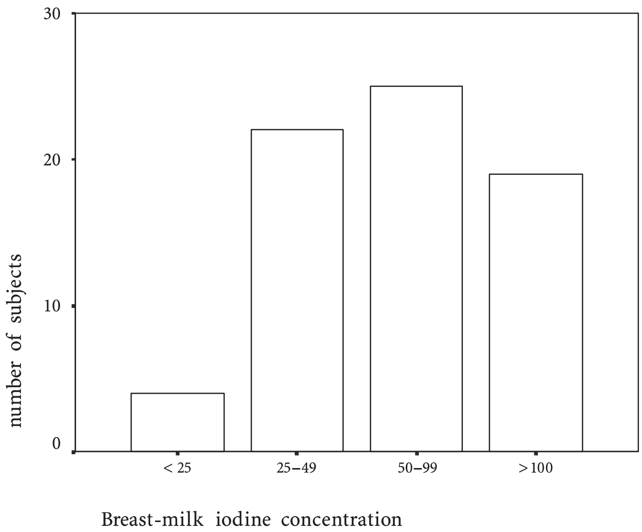

Fig. 3 Frequency distribution of breast-milk iodine concentrations (μg/l)

Serum studies

The median concentrations (and ranges) of neonatal TSH, Tg, FT3 and FT4 were 7.44 (1.06–30.54) mU/l, 71.62 (7.07–598.12) μg/l, 1.30 (0.64–4.29) pg/ml and 1.34 (0.65–2.52) ng/dl respectively. The corresponding levels for the mothers during labor were 2.19 (0.82–4.85) mU/l, 25.65 (0.38–185.18) μg/l, 1.31 (0.72–2.74) pg/ml and 1.23 (0.78–2.07) ng/dl respectively (Table 1).

The median neonatal serum concentrations of TSH and Tg were significantly higher than the corresponding maternal levels ($p < 0.0001$, $p < 0.0001$, respectively). There were no significant differences between the median neonatal concentrations and corresponding maternal levels of FT3 and FT4. There was a significant correlation between the newborn and maternal levels of FT3 (r: 0.32, $p < 0.05$) (Fig. 4).

Discussion

Iodine deficiency causes developmental abnormalities in all age groups. Most detrimental effects of inadequate iodine intake appear in pregnant women and in children [5, 23–26]. All degrees of iodine deficiency (based on median urinary iodine in μg/l; mild 50–99, moderate 20–49, severe < 25) affect the thyroid function of the mother and neonate, and the mental development of the child. The damage increases with the degree of the deficiency, with overt endemic cretinism as the severest consequence. Maternal hypothyroxinaemia during early pregnancy is a key factor in the development of the neurological damage in the cretin. Iodine deficiency results in a global loss of 10–15 intellectual quotient points at a population level, and constitutes the world's greatest single cause of preventable brain damage and mental retardation [27].

Turkey has long been known as a mild to moderate iodine deficiency country according to the figures obtained from previous epidemiological studies [9–14]. The total goiter prevalence in Turkey was as high as 30.5 %, and that of visible goiter 6.7 %. It was also showed that goiter prevalence did not fall below 2 % in any region after salt iodization, and it may remain up to 50 % in some regions [10]. Turkey is geographically a mountainous region with volcanic properties so lack of iodine in the soil and endemic goiter are expected findings. The status of iodine nutrition in Central Anatolia (Kayseri province and mountainous region) showed severe io-

Table 1 Median serum concentrations (and ranges) of Tg, TSH, FT3 and FT4 in the pregnant women during labor and in their neonates. Median urinary iodine (UI) concentrations (and ranges) of the mothers and their neonates on day 5 and median breast milk iodine (BMI) concentration (and ranges) on day 5

Parameter	Pregnant women during labor	Neonates (Cord blood serum)
Tg (ng/ml)	25.65 (0.38–185.18) (N < 30)	71.62 (7.07–598.12) (N: 2–54)
TSH (mU/l)	2.19 (0.82–4.85) (N: 0.5–4.8)	7.44 (1.06–30.54) (N: 1.0–28.9)
FT3 (pg/ml)	1.31 (0.72–2.74) (N: 2.30–6.60)	1.30 (0.64–4.29) (N: 0.2–2.4)
FT4 (ng/dl)	1.23 (0.78–2.07) (N: 0.8–2.3)	1.34 (0.65–2.52) (N: 2.0–4.9)
UI (μg/l)	30.20 (3.20–171.50) (N: 100–200)	23.80 (3.20–95.30) (N: 100–200)
BMI (μg/l)	73 (9.50–355.60) (N: 100–200)	

N reference values

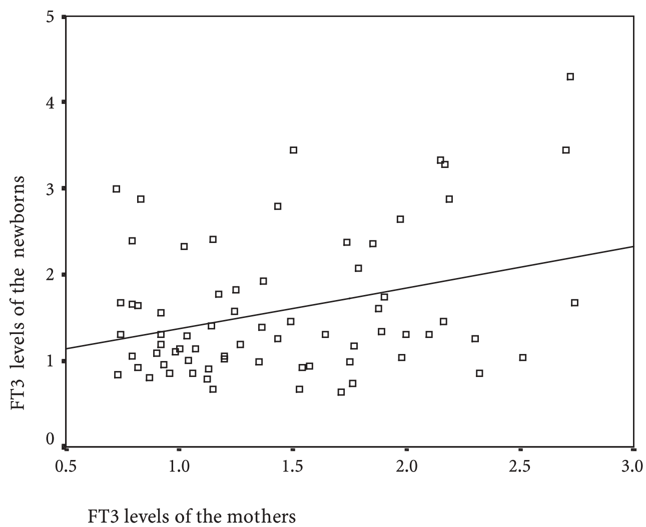

Fig. 4 Correlation between FT3 (pg/ml) levels of the mothers and their newborns (r: 0.32, $p < 0.05$)

dine deficiency in previous cross-sectional studies [9, 12].

In the present study, the median values of urinary iodine in mothers and their babies on the fifth day after delivery were 30.20 and 23.80 µg/l respectively. By using the criteria proposed by WHO/UNICEF/ICCIDD [7], these values indicate moderate iodine deficiency in both age groups. However, the median values below 100 µg/l, 50 µg/l and 25 µg/l indicating mild, moderate and severe iodine deficiency respectively have been established for adolescents and adults but have not been validated either for pregnant women or for neonates [7, 28]. The median urinary iodine in full term neonates is about 148 µg/l in Toronto, an iodine replete city [29]. Similarly, recent studies in Belgian neonates and infants aged 6 months to 3 years indicated that, in this age group, a median urinary iodine concentration of approximately 200 µg/l is required in order to insure optimal iodine nutrition [30]. Based on this information, it appears that neonates in the area under investigation are affected by a degree of iodine deficiency which is much more important than what could be expected on the basis of the criteria proposed by WHO/UNICEF/ICCIDD [7].

As in all other studies on the topic [31, 32], our results for the iodine content of breast milk show an important inter-individual variability. However, the mean and median values observed in this study are again much lower than in iodine sufficient areas [32], indicating that the status of the iodine nutrition of pregnant and lactating women is also clearly insufficient. This point is particularly important because the iodine supply of maternal origin plays a critical role in the constitution of the iodine stores of the fetus and neonate and because maternal hypothyroxinaemia during this critical period can induce irreversible brain damage in the progeny [1]. In our study, the iodine content of breast milk is much higher than that could be expected on the basis of the urinary iodine content of mothers. This is because the mammary gland is able to concentrate iodide during pregnancy and lactation, and this concentrating mechanism appears as an attempt to ensure an adequate supply of iodine to the newborn [33].

Thyroglobulin is the most abundant protein of the thyroid, providing the matrix for thyroid hormone synthesis. Normally, small amounts are secreted or leak from the thyroid into the circulation. When the thyroid is hyperplastic or injured, much larger amounts are released. The thyroid hyperplasia of iodine deficiency is regularly associated with increased serum Tg levels. In this setting, it reflects iodine nutrition over a period of months or years. In population studies, thyroglobulin is a sensitive marker of iodine deficiency and is occasionally considered as more sensitive than TSH [34, 35]. In the present study, median Tg levels of the mothers and their babies were 25.65 and 71.62 ng/ml respectively. In 30 newborns (42.9 %), cord Tg levels were above 54 ng/dl, the upper limit of normal for this age group [20]. In 29 mothers (41.4 %), serum Tg levels were above 30 ng/dl. High serum levels of Tg in both mothers and newborns reflect that Kayseri is an iodine deficient endemic area in Turkey [9, 12]. The pituitary secretes TSH in response to circulating levels of T4. The serum TSH rises when serum T4 concentrations are low, and falls when they are high. Iodine deficiency lowers circulating T4 and raises the serum TSH, so that iodine-deficient populations generally have higher serum TSH concentrations than do iodine-sufficient groups. The prevalence of neonates with elevated TSH levels is therefore a valuable indicator of the severity of iodine deficiency in a given population. None of the mothers had serum TSH levels above 5 mU/l but 27.14 % of newborns had cord serum TSH level above the cut off value of 10 mU/l. These results indicate moderate iodine deficiency and confirm that neonatal thyroid screening appears as a particularly sensitive index in the monitoring of iodine supply at a population level [21, 22].

In our study, most parameters showed an important inter-individual variability. We did not use any iodine containing antiseptic solutions during labor and after. And we studied the specimens with precise methods. This variability may be due to the eating behavior of the mothers. Despite the fact that in our country salt iodization is mandatory and 100 % of table salt has to be iodized, iodization of industrial salt is not enforced. Most of the families consume industrial salt instead of iodized table salt.

Salt iodization is arguably the most effective way to correct iodine deficiency in the long run. The goals for monitoring include a proportion of 90 % of households consuming effectively iodized salt, and urinary iodine in the normal range (median between 100–200 µg/l) [36]. An additional indicator could include the proportion of lactating women whose breast milk iodine concentration reaches a critical threshold of 100 µg/l [32]. The administration of iodine is recommended in early pregnancy (before the end of the 2nd trimester) for improvement of psychomotor test scores, cognitive development and head circumference for children relative to those provided iodine later in pregnancy or early postnatal life [37]. In marginally iodine-deficient areas, the administration of iodine (200 µg iodide/day) is recommended in pregnancy and lactation for improvement of thyroid function of mother and correction of iodine deficiency in baby [38]. The current WHO recommendations for daily iodine intake of 90 µg/day for infants during breastfeeding and 200–300 µg/day for lactating women was estimated to ensure that the iodine content of breast milk is in the range of 100–200 µg/l.

Salt iodization is currently the selected method for correcting iodine deficiency in Turkey. The program has been initiated in 1968 on a voluntary basis, when the use of potassium iodide was approved by the revised food codex. According to the recent figures provided by the Ministry of Health, iodized salt represented up to 75 % of the total production of salt by two main salt companies in 1999. Presently salt iodization is mandatory and 100 % of table salt has to be iodized. However, iodization of industrial salt is not enforced. Recently, the Ministry of Health initiated measures aiming at improvement of the iodine intake nationwide [10, 13].

As long as universal salt iodization is not systemically implemented in Turkey, special attention will need to be devoted to the protection of the two main target groups, i. e. pregnant and lactating mothers and young infants. If iodine deficient, these two age groups should receive supplementations with physiological quantities of iodine, for example by adding iodine to polyvitamins administered to these two age groups [26]. The data presented in this work show that iodine supplementation to pregnant and lactating women in Turkey, if any, is definitely insufficient to restore normal iodine intake in the breastfed infants. In addition some part of the country affected in the past by overt endemic cretinism, as well as in other countries in the world, iodine deficiency remains severe [9–14]. In such situations, urgent and more drastic short term measures can be justified from a public health point of view, such as the oral administration of iodized oil, as was the case recently in remote iodine deficient villages in Romania [39].

In conclusion, this regional cross sectional study in a part of Turkey affected by severe iodine deficiency in the past indicates that, in spite of the implementation of a mandatory salt iodization program, moderate, almost severe iodine deficiency persists in Central Anatolia with marked impairment of thyroid function in both pregnant, lactating women and neonates. This work confirms the hypersensitivity of the neonate to the effects of iodine deficiency with particularly elevated serum concentrations of thyroglobulin and TSH, indicating insufficient saturation of the T3 receptors of the developing brain and the risk of irreversible brain damage. Breast-milk iodine appears as an additional potential indicator for the degree of iodine deficiency.

As a whole this study is a strong argument not only for using neonatal thyroid screening as a monitoring tool of the status of iodine nutrition of a population but also for introducing iodine supplementation in addition to iodine fortification of salt as a temporary measure in areas were the degree of iodine deficiency implies a high risk of development of irreversible mental deficit in the growing infant.

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