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Urine and milk iodine concentrations in healthy and congenitally hypothyroid neonates and their mothers

Stężenie jodu w moczu zdrowych noworodków i noworodków z wrodzoną niedoczynnością tarczycy oraz w mleku i moczu ich matek

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Abstract

Introduction: In view of the high prevalence of Congenital Hypothyroidism (CH) in Iran, in this study we evaluated the role of iodine in the aetiology of CH by comparing urine and milk iodine concentrations in healthy and congenitally hypothyroid neonates and their mothers.

Material and methods: In a cross-sectional study, urinary iodine concentrations (UIC) in newborns with CH, as well as UIC and the milk iodine concentrations (MIC) of their mothers, were measured and compared with a control group. The lower, mid, and upper range of UIC for neonates and lactating mothers was considered to be < 150 μg/L, 150–230 μg/L, and > 230 μg/L, and lower, mid, and upper range of MIC was considered to be < 150 μg/L, 150–180 μg/L, and > 180 μg/L, respectively.

Results: The median UICs in subjects with CH (n = 68) and healthy subjects (n = 179) were 300.5 and 290.5 μg/L, respectively (P > 0.05). The median UICs in the case and control groups were 150 and 130 μg/L, respectively (P > 0.05). The median MIC in the case group was higher than in the control group (210 μg/L *v.* 170 μg/L, P < 0.05).There was a positive correlation between newborn UIC and MIC. There was no significant correlation between newborn UIC and serum TSH, maternal UIC and maternal MIC, or newborn UIC and serum TSH.

Conclusions: There is no inadequacy in iodine intake in the studied population. Iodine excess could be a possible risk factor for CH, but there were findings, such as lack of correlation between maternal MIC and UIC, and the median neonatal UIC, which was similar in the two groups, so, drawing conclusions should be done with some caution and requires further studies.

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Key words: *congenital hypothyroidism, milk, urine, iodine*

Streszczenie

Wstęp: Częste występowanie wrodzonej niedoczynności tarczycy (CH, *congenital hypothyroidism*) w Iranie skłoniło autorów do oceny roli jodu w etiologii CH, opierając się na porównaniu jego stężenia w moczu zdrowych noworodków i noworodków z wrodzoną niedoczynnością tarczycy oraz w mleku i moczu ich matek.

Materiał i metody: W tym przekrojowym badaniu zmierzono stężenie jodu w moczu (UIC, *urinary iodine concentration*) noworodków z CH oraz UIC i stężenie jodu w mleku (MIC, *milk iodine concentration*) ich matek, a następnie porównano je z wynikami otrzymanymi w grupie kontrolnej.

Wartości UIC zmierzone u noworodków i karmiących matek podzielono na 3 kategorie: niskie UIC < 150 μg/l, średnie — 150–230 μg/l i wysokie > 230 μg/l. Analogiczne kategorie przyjęto dla MIC: niskie < 150 μg/l, średnie 150–180 μg/l i wysokie > 180 μg/l.

Wyniki: Mediana UIC u noworodków z CH (n = 68) i u zdrowych noworodków (n = 179) wynosiła odpowiednio 300,5 i 290,5 μg/dl, (P > 0,05). Mediana UIC w grupach badanej i kontrolnej wynosiła odpowiednio 150 i 130 μg/l (P > 0,05). Mediana MIC w grupie badanej była większa niż w grupie kontrolnej (210 μg/l *v.* 170 μg/l, P < 0,05). Stwierdzono dodatnią korelację między UIC u noworodków i MIC u ich matek. Nie wykazano wyraźnej zależności między UIC i stężeniem TSH w surowicy u noworodków oraz UIC I MIC u matek.

Wnioski: Spożycie sodu w badanej populacji było prawidłowe. Nadmierna podaż sodu może być czynnikiem ryzyka CH, jednak w badaniu wykazano brak korelacji między MIC I UIC u matek i podobne wartości mediany UIC u noworodków w obu grupach, dlatego do sformułowania jednoznacznych wniosków potrzebne są dalsze badania.

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Słowa kluczowe: *wrodzony hipotyreoidyzm, mleko, mocz, jod*

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Introduction

Iodine is essential for thyroid hormone synthesis and, accordingly, is required for normal development, growth, and metabolism, and it is well known that both iodine deficiency and iodine excess affect neonatal thyroid function [1]. A lack of thyroid hormone for more than a few weeks during brain development in utero or during the first years of life may permanently harm brain function, and breastfed infants are reliant on adequate maternal dietary iodine intake [2]. Adequate maternal dietary iodine intake is required for normal foetal brain development and for the continued neurodevelopment of breast-fed infants [3–4]. Congenital hypothyroidism is the most common cause of preventable mental retardation, and around the world the most common cause of congenital hypothyroidism is iodine deficiency [5–6], but in most of the developed world and areas of adequate environmental iodine, factors other than iodine deficiency are responsible for the disorder, such as genetic factors, thyroid autoimmunity, and iodine excess, especially in formerly iodine-deficient areas [7–9].

Many studies have demonstrated that iodine excess is a risk factor for CH [10].The foetus and newborn can be exposed to high maternal iodine concentrations either by crossing the placenta perinatally, or postnatally by secretion of iodine into breast milk [11]. Iodine excess has an antithyroid effect due to the so-called Wollf--Chaikoff effect; it blocks the uptakes of iodine by the thyroid gland and leads to reduced T4 and increased TSH [12–13].

Major progress has been made toward elimination of iodine deficiency in Iran, and according to the study of Azizi et al., Iran has reached a sustainable control program for iodine deficiency [14], as also reported by the WHO [15].

Screening programs for congenital hypothyroidism, in addition to early detection and treatment of the disorder, provide the opportunity to investigate the aetiology and the pathogenesis of CH. According to the reports of CH screening in Iran, CH is more prevalent in this region. It is detected at a rate of 1 per 914 live births in Tehran, 1 per 1433 in Fars, and 1 per 370 in Isfahan [16–18]. Nowadays, CH screening is established in Iran as a nationwide program, but considering its high prevalence it seems that it is necessary to investigate the possible contributors of CH in our region. There have been studies in Isfahan and in other parts of the country which have indicated that urine and milk iodine concentrations are within the acceptable range [19–21], but in Isfahan at the time of CH screening, the status of iodine in newborns and their mothers had not studied been. Therefore, the aim of this study was to determine the role of iodine, as a major environmental risk factor, in the aetiology of CH in Isfahan by comparing urine and milk iodine concentrations in healthy and congenitally hypothyroid neonates and their mothers.

Material and methods

During this cross-sectional study, from September 2006 to February 2007, urinary iodine concentrations (UIC) in newborns with CH as well as UIC and Milk iodine concentrations (MIC) of their mothers were measured and were compared with a control group. Subjects in both the case and control groups were selected by a simple sampling method from newborns and their mothers during a CH screening program in Isfahan. According to the CH screening protocol, neonates with abnormal screening results (TSH > 10 mIU/L by heel-prick method) were re-examined, and newborns with abnormal T4 (< 6 μg/dL) and TSH (> 10 mIU/L) levels on their second measurement were diagnosed as CH patients and referred to Isfahan Endocrine and Metabolism Research Centre for treatment and regular follow up [18]. Seventy-six CH patients and their mothers were invited (case group), and 184 neonates and their mothers with normal screening results were also invited (control group). The participants in the control group were matched to the case group according to age and socioeconomic condition. All selected neonates were exclusively breast fed until laboratory measurement. Mothers with a history of pre- or postnatal exposure to excessive amounts of iodine, such as thyroid hormone ingestion or use of iodine-containing topical antiseptics, maternal consumption of goitrogens and/or thyroid affecting medications, known systemic disorders, palpable goiter, or thyroid disorder and preterm infants (< 37 weeks' gestation), neonates with history of hospitalization, exchange blood transfusion because of neonatal hyperbilirubinaemia, were excluded. Written consent was obtained from all participants. Blood and urine samples were taken from newborns. Urine, blood, and milk samples were also collected from the mothers of the newborns. Neonatal and maternal urine and maternal breast milk samples were obtained on days 14 to 28 from birth. Spot urine and breast milk samples were collected for the measurement of iodine concentrations. Urine samples were kept at –20°C until assayed at the end of the study. Thyroid function tests (TSH and T_4) were performed in mothers also.

Lower, mid, and upper ranges of UIC for neonates and lactating mothers was considered to be < 150 μg/L, 150–230 μg/L, and > 230 μg/L and lower, mid, and upper ranges of MIC were considered to be < 150 μg/L,

Table I. *Characteristics and laboratory data of case and control groups*
Tabela I. *Charakterystyka grup badanej i kontrolnej oraz wyniki badań laboratoryjnych w obu grupach*

	Case group n = 68		Control group n = 179		P value
	Mean ± SD	Median	Mean ± SD	Median	
Weight [gr]*	2958.2 ± 482.4	2800.0 (2400–4100)	3228.4 ± 468.5	3070.0 (2700–4070)	NS
Height [cm]	52.9 ± 3.1	52.5 (46–59)	52.1 ± 1.6	52.0 (46–58)	NS
Head circumference [cm]	37.2 ± 1.4	37.5 (31–39)	37.6 ± 0.9	37.5 (33–39)	NS
Screening TSH [mIU/L]	22.3 ± 27.2	11.5 (10–100)	6.4 ± 2.4	5.4 (4–22)	0.00
TSH mother [mIU/L]	2.3 ± 1.8	2.0 (1.1–6.4)	1.3 ± 1.0	1.00 (1–6.6)	0.00
T4–mother* [μg/dL]	9.2 ± 2.9	8.5 (6.2–12.8)	9.4 ± 2.3	9.2 (6.5–13.1)	NS
Urine iodine newborn [μg/L]	280.4 ± 120.0	300.0 (10–420)	280.6 ± 100.9	290.5 (30–360)	NS
Urine iodine mother [μg/L]	160.9 ± 100.1	150.0 (20–400)	140.4 ± 70.4	130.0 (20–400)	NS
Milk iodine mother [μg/L]	220.6 ± 80.1	210.0 (70–370)	180.1 ± 50.3	170.0 (60–320)	0.00

*distribution was normal; mean was compared

150–180 μg/L, and > 180 μg/L, respectively. In addition, we considered the recommendations of the WHO, UNICEF, ICCIDD [22], and one other study in Iran [21] by determining the proportion of participants with UIC < 50 μg/L, 50–100 μg/L, and 100–150 μg/L and MIC < 50 μg/L and 50–150 μg/L.

Laboratory methods

After acid digestion of urine and alkaline incineration of milk samples, iodine concentrations were determined by the Sandell–Kolthoff method [23]. Serum TSH and T_4 concentrations were determined by ImmunoRadioMetricAssay (IRMA) and RadioImmunoAssay (RIA) using Kavoshyar (Tehran-Iran) kits.

Statistical analysis

Data were analyzed using SPSS 11.0 for Windows. χ^2, paired t-test, Wilcoxon, and Pearson correlation, and Spearman's correlation tests were used for statistical analysis. P value less than 0.05 was considered statistically significant. The normal distribution of continuous variables was verified by Kolmogorov-Smirnov test.

Results

In this study, from the invited CH neonates and mothers, 68 CH neonates with normal thyroid ultrasonography and their mothers and 179 neonates and their mothers in the control group enrolled in the study. Mean maternal age in the case and control groups were 26.2 ± 6.1 years (19–35) and 25.9 ± 5.7 years (18–34), respectively (P > 0.05). Mean age of neonates in the case and control groups at the time of the study were 20.8 ± 7.2 days and 16.2 ± 4.8 days, respectively (P < 0.05). Characteristics and laboratory data (mean = /– SD or median) of the case and control group are presented in Table I. The median of newborns and mothers UIC and mothers MIC (both case and control) was 300 μg/L (10–460), 130 μg/L (20–400), and 180 μg/L (60–370), respectively. The proportions of breast milk iodine and maternal and neonatal urine iodine according to our classification are presented in Tables II and III.

According to the Pearson test, there was positive correlation between newborn UIC and MIC (P < 0.05, r = 0.015) and there was no correlation between newborn UIC and serum TSH. Maternal UIC did not correlate with maternal MIC, newborn UIC, and serum TSH.

Discussion

In this study, the effect of iodine status in newborns and their mothers, the two sensitive groups in this field, on the aetiology of CH was studied during a CH screening program in Isfahan. The findings of our study indicated that the median of UIC in the two groups and MIC was within the acceptable range for an iodine sufficient area, a fact which was also reported earlier [14]. It seems that iodine excess is thought to contribute to the high prevalence of CH in this region because both the median of mothers MIC in the case group and the proportion of mothers with iodine excess according to our classification was higher than the control group.

Within a population, newborns and pregnant or lactating women are the groups most vulnerable to iodine deficiency. According to the latest report from the NHANES study and another study in China, despite an effective iodized salt program, pregnant and lactating women in some areas may still risk deficiency and

Table II. *Proportions of different values of urinary iodine in case and control groups*

Tabela II. *Odsetek osób w grupach badanej i kontrolnej, u których stężenie jodu w moczu mieści się w poszczególnych przedziałach wartości*

Urinary iodine concentration [μg/L]	Neonates in case group n (%)	Neonates in control group n (%)	Mothers in case group n (%)	Mothers in control group n (%)
< 50	1 (1.6%)	2 (1.2%)	3 (4.8%)	2 (1.2%)
< 100	2 (3.2%)	5 (3.0%)	15 (24.2%)	34 (20.7%)
100–150	8 (12.9%)	13 (7.9%)	13 (21%)*	60 (36.6%)
150–230	13 (21.0%)	41 (25%)	23 (37.1)	49 (29.9%)
≥ 230	39 (62.9%)	105 (64%)	11 (17.7%)	21 (12.8%)
	62 (100%)	164 (100%)	62 (100%)	164 (100%)

*P = 0.02

Table III. *Proportions of different values of breast milk iodine in case and control groups*

Tabela III. *Odsetek osób w grupach badanej i kontrolnej, u których stężenie jodu w mleku mieści się w poszczególnych przedziałach wartości*

Breast milk iodine concentration [μg/l]	Mothers in case group n (%)	Mothers in control group n (%)
< 50	0 (0%)	0 (0%)
50–150	8 (12.9%)*	45 (27.4%)
150–180	10 (16.1%)	41 (25%)
≥ 180	44 (71%)**	78 (47.6%)
	62 (100%)	164 (100%)

*P = 0.02

**P = 0.001

need further supplements [24, 25]. Studies carried out in Iran after the salt iodization program have indicated adequate UIC and MIC among pregnant and lactating women and newborns [19–21]. Ordookhani et al., in a similar study among healthy neonates and their mothers, reported that median UIC and MIC was within the appropriate range [26].

The median breast Milk iodide level in a 1984 sample of 37 U.S. women was 178 μg/L [27] and 155 μg/L in another study in Australia [28]. Gons et al., in their study among 151 Dutch newborns with and without CH, reported that the median value of UIC was 31 μg/24 h [29].

In our study, the median UIC in all neonates and their mothers was not different in the case and control groups, but the median MIC was significantly higher in mothers of CH neonates, and it was in the upper range of MIC values (180). It was higher than the two previously mentioned studies in Iran [21, 26], and it was similar to the median MIC in US women [27]. The proportion of neonates and mothers with upper range of iodine, both in the case and control groups, was higher than those with lower range, and iodine excess was more prevalent in mothers of hypothyroid neonates than in the control group, which indicates the possible role of iodine excess in the aetiology of CH. In the study of Bazrafshan et al.,UIC < 100 μg/L and MIC < 50 μg/L was presented in 16% and 19% of their studied population, respectively, which was higher than in our study [21].Ordookhani et al. reported that MIC was < 150, 150–180, and > 180 μg/L in 52.4, 11.9, and 35.7% of mothers, respectively. Compared with our results, iodine excess and deficiency was lower and higher, respectively, in the case and control groups [26]. The proportion of different neonatal UIC ranges was similar to those seen in our study, but in the case of maternal UIC classification, in our study UIC < 150 and > 230 were lower and higher, respectively.

The difference between our results and other studies in Iran may be due to the fact that our study was held later, so the duration of using iodized salt was longer; however, it may also be explained by differences in genetic background, environmental factors, and the different biochemical, clinical, and epidemiological methods which have been applied, especially for iodine measurement and classification of iodine range. Despite increasing numbers of studies examining UIC and MIC, no consistent recommendations have been made for optimal levels of iodine in breast milk or urine in infants and in pregnant and lactating women [2, 30]. In the current study, iodine range classification was a combination of WHO, UNICEF, and ICCIDD recommendations and prior studies which were performed in our region [21, 22].

There are controversial results regarding the effect of iodine excess on CH: some studies demonstrated that

it causes a transient form of CH [31] but others propose that hyperthyrotropinaemia as a result of excessive iodine in some cases might not be transient [32]. In an aetiological study of transient CH in Iran, Ordookhani et al. reported that the occurrence of the most frequent findings among transient CH patients was iodine contamination and excessive UIC [33]. Whereas, according to the study of Nishiyama et al., excessive iodine intake in mothers results in persistent hyperthyrotropinaemia [32]. In our study, the studied neonates in the case group consisted primarily of diagnosed CH patients with normal thyroid ultrasonography.

In this study there was no correlation between neonatal serum TSH concentration and neonatal or maternal UIC or MIC, which was in accordance with the study of Ordookhani et al. The findings of Chan et al. were different to those of our study; they reported that neonatal TSH levels were positively correlated with higher breast milk iodine but that there was no significant correlation between neonatal TSH levels and the mother's urine iodine content, as in our study [34]. The differences may be due to the fact that breast milk iodine was significantly correlated with urine iodine in micrograms per gram of creatinine but not with urine iodine measured in micrograms per litre, and in this study both UIC and MIC were measured in micrograms per litre. In addition, UIC in spot urine samples is not a good indicator of neonatal thyroid function [20].

In our study, the median MIC was significantly higher in the case group and there was a positive correlation between MIC and neonatal UIC, but the median of neonatal UIC was not significantly different in the case and control groups. This may be explained by the fact that during the breast feeding period iodine is concentrated in milk glands more than before the breast feeding period. This will cause a significant increase in iodine concentration in milk following a small increase in the iodine content of the whole body. This may gradually result in a higher intake of iodine by the newborn, and an inhibitory effect of iodine (Wolf Chiakoff Effect) may cause CH [12, 35, 36]. Another explanation is that especially severe CH patients drink less milk, giving a reduction in urinary iodine excretion and also in CH patients with thyroid agenesis iodine absorption from the intestinal tract decrease [37].

The age at collection also influences urinary iodine excretion [38].The mean age of collection for the case group was 20.8 days and 16.2 days for the control group. It was higher in the case group because it takes time after recall to make a final diagnosis of CH. However, by analysis of covariance, we calculated that the difference in the age of collection had no effect on the UIC of the two studied groups. Nevertheless, according to some studies, although iodide levels in breast milk correlate with dietary iodine, iodide levels in breast milk do not correlate with the age of the infant (i.e. stage of lactation) [27].

There was no correlation between maternal UIC and MIC in our study, which was in contrast to the results of Bazrafshan et al. and Ordookhani et al.

In conclusion, our findings indicate that iodine excess could be a possible risk factor for CH. However, there were findings, such as lack of correlation between maternal MIC and UIC, the median neonatal UIC which was similar in two groups, etc., which were mentioned, and although we have an explanation for the findings, it seems that drawing conclusions in this field should be done with some caution. So, we recommended that further studies with larger sample sizes are needed, and we should also investigate the source of iodine excess. In addition, in order to draw accurate conclusions in the field of CH aetiology in our community, we should study the role of genetics and autoimmunity, in which iodine excess could also be responsible.

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