RESEARCH

Lower educational status interferes with maternal iodine intake during both pregnancy and lactation

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Abstract

Objective: To investigate factors affecting conscious iodine intake among pregnant and lactating women in a rural area in Hungary.

Methods: Pregnant women were studied and followed during lactation. Urinary and breast milk iodine concentration (UIC and MIC) were measured by inductively coupled plasma mass spectrometry. Potential interfering factors, including age, educational status and smoking were assessed.

Results: During pregnancy and lactation, mild iodine deficiency was observed; median UIC were 66 and 49 μg/L, respectively. Educational status was found to be a strong determinant of both iodine nutrition and smoking status during pregnancy ($P < 0.01$ and $P < 0.001$) and lactation ($P < 0.001$ and $P < 0.01$). While smoking and non-smoking lactating mothers had similar concentrations of urinary iodine (median UIC: 47 and 51 μg/L, $P = 0.95$), the breast milk of smoking mothers contained less iodine (median MIC: 150 and 203 μg/L, $P = 0.03$).

Conclusions: Both low iodine intake and smoking contribute to the higher risk of iodine deficiency in women with lower educational status. In smokers, MIC is often low in spite of normal UIC, presumably due to the iodine transport blocking effect of the cigarette smoke towards breast milk; normal UIC may be misinterpreted as sufficient iodine supply towards the child. Antenatal health promotion strategies should focus on young women with lower educational status, even in regions where sufficient iodine intake has been achieved in non-pregnant adults.

Introduction

While the number of iodine-deficient countries has decreased worldwide, mild iodine deficiency still exists in Europe (1, 2). Adequate iodine intake during pregnancy is a prerequisite for thyroid hormone synthesis and is essential for foetal brain development (3, 4). The recommended daily intake of iodine in non-pregnant adults is 150 μg, while 250 μg is required during pregnancy and lactation (5, 6). Pregnancy induces changes in thyroid function and

iodine metabolism: the level of thyroxine-binding globulin increases in response to elevated oestrogen levels, thyroid-stimulating hormone receptors (TSHR) are stimulated by human chorionic gonadotropin, thyroid hormone and iodine are transported towards the foetus through the placenta, and renal clearance of iodine increases due to the higher glomerular filtration rate. All these contribute to the higher demand for iodine (7, 8). Type 3 deiodinase enzyme of the placenta increases the degradation of thyroxine (T4) towards inactive reverse triiodothyronine (rT3) (4, 9). If maternal dietary iodine intake is not adjusted appropriately, iodine sufficiency of the non-pregnant state easily converts into iodine deficiency, or mild iodine deficiency progresses towards moderate to severe deficiency (10). Even mild maternal iodine deficiency impairs the cognitive development of the child (11, 12). In mild iodine deficiency, thyroid stimulation leads to the preferential secretion of triiodothyronine (T3) over T4 without elevation of TSH level (13, 14). Maternal hypothyroxinaemia during pregnancy may be associated with impaired neurodevelopment of the foetus, especially from early to mid-gestation, when the foetus is fully dependent on maternal thyroxine (13, 14).

During lactation, iodine is secreted into the milk. Breast milk is the only source of iodine for the breastfed infant, being vital for normal infant thyroid function and thus, for brain development (15). Mammary glands can concentrate and secrete large amounts of iodine at the expense of the mother, which explains the increased maternal iodine requirements throughout nursing (16). For pregnant and lactating women living in iodine-deficient areas, the regular use of iodine-containing multivitamins or other supplements is a must to achieve optimal iodine intake, and ensure the normal neurodevelopment of the foetus and the breastfed infant (17).

Mild iodine deficiency sensitises to certain endocrine disruptors, for example, thiocyanate (18). Thiocyanate inhibits the sodium-iodide symporter (NIS), which is responsible for the active uptake of iodide by the thyroid, the gastrointestinal tract, the placenta and the lactating mammary glands (19). Thiocyanate accumulates in the blood and tissues of smokers, impairs iodine uptake and worsens iodine deficiency (20). Despite recommendations, some women continue to smoke during pregnancy and lactation (21, 22).

Measurement of the median urinary iodine concentration (UIC) is the recommended method to assess iodine status at the population level (23). A median concentration of more than 150 and 100 µg/L urinary iodine indicates iodine sufficiency of pregnant and lactating women, respectively (6). In spot urine samples, standardising the urinary iodine concentration for urinary creatinine is useful in correcting for the influence of fluid intake (24), especially in pregnant women.

The aim of this study was to investigate factors affecting conscious iodine intake among pregnant and lactating women living in a rural area in Hungary.

Subjects and methods

Subjects

One hundred and twenty-three healthy pregnant women living in a rural area of North-East Hungary were enrolled in the study with consecutive sampling. The protocol was approved by the Institutional Ethics Committee of the University of Debrecen and by the Human Reproduction Committee of the National Medical Research Council. After informed consent, spot urine samples were collected for UIC measurements. Thyroid volume measurements were performed by ultrasound: each lobe of the thyroid gland was assessed separately by measuring the three main diameters, and the total volume of the thyroid was calculated by the $\pi/6 \times$ height $\times$ width $\times$ depth formula. The upper limit of normal thyroid volume was 18 mL (25, 26). Using a questionnaire, awareness about the health importance of iodine, regular intake of supplementary iodine (iodised salt and/or iodine-containing multivitamin), list of current medications if any, educational status, age, parity and smoking habits were assessed. In Hungary, 8 years of mandatory elementary school education is typically followed by optional secondary school (high school) and subsequently, college may follow; eight or less completed elementary school years have been considered low educational level. Smoking status was confirmed by the measurement of urine cotinine concentration.

During the postpartum nursing visit, spot urine and breast milk samples were collected for the same measurements as during pregnancy, and women were asked to fill out the same questionnaire again about their intake of supplementary iodine and current smoking practices.

Laboratory measurements

Urine and breast milk samples were stored at −20°C until used. Iodine concentration was measured by inductively coupled plasma mass spectrometry (ICP-MS). Spot urine samples were diluted 10 times with de-ionised 18 MΩ

water (MilliQ, Millipore) before the analysis. One millilitre aliquots of the milk samples were digested with 5 mL of 0.5% (v/v) ammonia solution in a Milestone Start D Microwave Digestion System (Milestone Srl, Sorisole, Italy) at 80°C for 5 min. The resulting solution was diluted to 10 mL with de-ionised 18 MΩ water. Germanium, rhodium and platinum were used as internal standards (100 µg/L). The digested and/or diluted samples were analysed by a Thermo Scientific XSeries 2 ICP-MS (Thermo Fisher Scientific Inc.) with a hexapole collision/reaction cell (CCT).

Self-reported non-smoker status has been confirmed by measurement of the nicotine metabolite cotinine in the urine by gas chromatography-mass spectrometry (GC-MS) as described (27). Urine creatinine levels were measured on the day of collection by Jaffé's method using a Cobas 6000 analyser (Roche Diagnostics Ltd.).

Statistical analysis

Statistical analysis was performed by STATISTICA 12 software (Statsoft Inc. Tulsa, OK, USA). The distribution of continuous variables was checked by the Kolmogorov–Smirnov test. Due to the non-normal distributed data, the Mann–Whitney U test or the Kruskal–Wallis H test with *post hoc* tests were used to compare continuous variables between two or more subgroups, respectively.

Results were expressed as medians and 25th and 75th percentiles (interquartile range, IQR). Binary variables were analysed by chi-square or Fisher's exact tests. For analysis of the relationship between urinary and breast milk iodine Spearman's rank-order correlation was performed. P values below 0.05 were considered statistically significant.

Results

Of the 123 women invited, pregnancy and lactation spot urine samples, thyroid ultrasound result and complete response to the questionnaire were available for 100 women. None of them were on thyroid medications. The main characteristics of the studied pregnant women, as well as UIC values in pregnancy and lactation, and milk iodine concentrations are shown in Table 1. Based on the criteria defined by the WHO, we found mild maternal iodine deficiency in pregnancy in the studied population. The goitre rate in pregnant women was 11% by ultrasound.

Seventy-three per cent of the pregnant women were aware of the health importance of iodine, mainly learning this fact from the health visitor (30/73; 30% of all), the gynaecologist (24/73; 24% of all) or from the media (22/73; 22% of all). The health visitor system was introduced in 1915 and sustained since than in Hungary; the health visitor is a state financed, community-based nurse who

Table 1 Main characteristics of the study population ($n = 100$) and parameters of iodine supply.

Characteristics	Values	
Age (years), median (IQR)	25 (20–29)	
Education, %		
≤8 years	55	
>8 years	40	
Not known	5	
Unemployment, %	87	
Parity, %		
Nulliparous	40	
Multiparous	60	
Previous miscarriage, %	19	
	Pregnancy	**Lactation**
Gestational week at sampling, median (IQR)	20 (15–28)	NA
Preterm birth (<37 weeks), %	11	NA
Weeks after delivery at sampling, median (IQR)	NA	7 (6–9)
Use of iodised salt, %	48	43
Use of any multivitamin, %	79	33
Use of iodine-containing multivitamin, %	52	20
Smoking, %	27	25
UIC (µg/L), median (IQR)	66 (31–108)	49 (32-76)
UIC (µg/g creatinine), median (IQR)	57 (35–120)	58 (40–92)
MIC (µg/L),[a] median (IQR)	NA	188 (116–257)

[a]$n = 93$.
IQR, interquartile range; MIC, milk iodine concentration; UIC, urinary iodine concentration.

provides individualised advice for each pregnant woman from the detection of pregnancy until 6-year age of the child, schedules gynaecological and later paediatric office visits. While overseeing pregnancy, lactation and childcare, supports the families with advice. Of note, state-provided pregnancy-benefits and nursing-benefits and payments require certain number of health visitor consultations documented. In the rural area with 87% unemployment among women (Table 1), this guarantees their presence on health visitor consultations.

Pregnant women who were aware of the importance of iodine intake were more often iodised salt users in their households (61% vs 17%, $P < 0.001$); however, there was no difference in the use of iodine-containing pregnancy multivitamins (53% vs 50%). The iodine content of pregnancy multivitamins was uniformly 150 μg daily in the form of potassium iodide. The household iodised salt coverage rate was low (Table 1).

During lactation, iodine-containing pregnancy multivitamin usage was less frequent than during pregnancy (33% vs 79%, $P < 0.001$, Table 1). None of the subgroups formed on the basis of iodine intake was iodine sufficient according to the median UIC (Table 2). One hundred and fifty micrograms of iodine supplementation daily (with or without the use of iodised salt) increased significantly the creatinine standardised UIC, compared with non-users during pregnancy (Table 2).

Of the pregnant women, 27% smoked despite being advised against this. Smoking in pregnancy had no significant effect on urinary iodine excretion (Table 2). When the subgroup of women who continued ($n = 27$) smoking during pregnancy was compared to those who stopped ($n = 30$) smoking (and thus, are in the non-smoker group in other parts of the analysis), smokers were younger (median age: 20 years vs 28 years, $P < 0.01$), less educated (ratio of women with ≤8 years education 88% vs 29%, $P = 0.0001$), and were more frequently exposed to passive smoking (74% vs 45%, $P = 0.04$).

The effect of educational status on awareness about the importance of iodine, iodine supplementation and smoking are shown in Table 3. Less-educated pregnant women were younger, used iodine supplementation to a lesser extent, smoking was found to be more common among them, and had a higher risk of iodine deficiency according to UIC. Low educational status resulted in abandoning iodine-containing pregnancy supplements following delivery compared to the more educated subgroup (90% vs 30%, $P < 0.001$).

Iodine content of the breast milk, but not urinary iodine concentration, was significantly lower in smokers (Table 2). In non-smokers, there was a significant positive correlation between creatinine-standardised urinary iodine concentration and breast milk iodine ($r_s = 0.43$, $P < 0.001$), whereas in smokers the correlation was missing ($r_s = -0.14$, $P = 0.525$).

Discussion

Mild iodine deficiency remains a public health burden in some industrialised countries in Europe, especially during pregnancy and lactation (1) when iodised salt usage alone does not cover the increased iodine demand (28). Iodine deficiency has been shown to interfere with the brain development of the foetus (3, 11, 12, 29).

Main characteristics of the rural areas in North-East Hungary are low socioeconomic status, low educational status and high unemployment rate. This region is iodine

Table 2 The effect of iodised salt, iodine-containing multivitamin use, and smoking on the iodine status during pregnancy and lactation ($n = 100$). Data shown as median (interquartile range).

	Pregnancy		Lactation		
	UIC (μg/L)	UIC (μg/g creatinine)	UIC (μg/L)	UIC (μg/g creatinine)	MIC (μg/L)[a]
Iodine supplementation					
None	40 (15–84)	36 (24–64)	43 (31–61)	47 (32–88)	157 (92–227)
Only iodised salt	72 (25–118)	49 (35–90)	50 (32–90)	62 (43–91)	213 (134–261)
≥150 μg iodine/day	75 (38–111)	77 (42–126)[b]	62 (37–81)	79 (53–93)	236 (208–304)[c]
P value[d]	0.071	<0.005	0.344	0.121	<0.001
Smoking					
Non-smokers	74 (36–112)	61 (36–126)	51 (31–80)	59 (40–91)	203 (119–280)
Smokers	40 (26–90)	48 (32–69)	47 (37–59)	52 (36–111)	150 (92–211)
P value[e]	0.069	0.130	0.951	0.691	0.030

[a]$n = 93$; [b]*Post hoc* test results: significant difference compared to the subgroup of non-users, $P < 0.005$; [c]*Post hoc* test results: significant difference compared to the subgroup of non-users, $P < 0.001$. [d]Kruskal–Wallis *H* test; [e]Mann–Whitney *U* test.
MIC, milk iodine concentration; UIC, urinary iodine concentration.

Table 3 Education level and iodine nutrition during pregnancy and lactation.

	Education		*P* value[a]
	≤ 8 years, *n* = 55	> 8 years, *n* = 40	
Age (years), median (IQR)	21 (18–27)	27 (25–30)	<0.001
Awareness about iodine, %	62	88	<0.01
Nullparity, %	33	55	0.03
Previous miscarriage, %	20	15	0.530
Pregnancy			
Gestational weeks, median (IQR)	18 (15–26)	20 (15–28)	0.718
Use of iodised salt, %	35	73	<0.001
Use of pregnancy supplements, %	71	98	<0.001
Use of iodine-containing supplements, %	55	53	0.844
Smoking, %	38	8	<0.001
UIC (µg/L), median (IQR)	47 (30–84)	87 (43–150)	<0.01
UIC (µg/g creatinine), median (IQR)	50 (35–68)	104 (45–157)	<0.001
Preterm birth (<37 weeks), %	11	13	0.811
Lactation			
Weeks after delivery, median (IQR)	8 (6–9)	7 (6–8)	0.658
Use of iodised salt, %	20	84	<0.001
Use of pregnancy supplements, %	14	64	<0.001
Use of iodine-containing supplements, %	6	35	<0.001
Smoking, %	36	10	<0.01
UIC (µg/L), median (IQR)	47 (32–66)	61 (36–90)	0.100
UIC (µg/g creatinine), median (IQR)	45 (35–66)	82 (52–111)	<0.005
MIC (µg/L),[b] median (IQR)	171 (99–227)	241 (199–311)	<0.001

[a]for continuous variables Mann–Whitney *U* test, for binary variables chi-square test and, in case of groups *n* < 10, Fisher's exact test were used; [b]*n* = 93.
IQR, interquartile range; MIC, milk iodine concentration; UIC, urinary iodine concentration.

deficient due to the low iodine content of the soil and natural water supplies (30); therefore, the iodine content of local, home-grown food is also low. Residents of this region are at higher risk of iodine deficiency, especially vulnerable groups like pregnant and breastfeeding women. Despite the information received about their increased iodine needs during pregnancy, the majority of women in the study population were not taking sufficient iodine. This finding is consonant with that of a recent study, where a programme for pregnant women about the importance of iodine nutrition did not have a significant effect on their iodine status (31). In Hungary, pregnancy multivitamins are recommended as part of the routine obstetric care. This information has been made available to the general public at the website of the Hungarian Society of Endocrinology and Metabolism (32). The online health information in their native language on the internet could be a tool for educating women in childbearing age about the importance of iodine (33). At the time of this study, all but one pregnancy multivitamins on the Hungarian market contained iodine.

Our results suggest that the use of iodised salt is the conscious form of iodine supplementation, while pregnancy supplement selection was not based on iodine content. In the present study, any form of iodine supplementation alone or in combination were not sufficient to achieve adequate maternal iodine intake during pregnancy and lactation. In agreement with previous findings by our (26, 27) and other (29, 34) groups, this result points to the fact that the iodised salt usage alone or starting iodine-containing pregnancy supplements after conception do not uniformly cover the increased iodine requirement during pregnancy, particularly in women who were iodine deficient before pregnancy.

We found that during lactation the iodine concentration of breast milk, but not UIC, reflected maternal iodine intake. Maternal iodine supplementation is important even in the period of complementary feeding, since recent findings suggest that iodine supplementation of the breastfeeding mother is more effective in improving infant iodine status than direct supplementation to the infant (35). Despite the fact that most women in the studied population stopped using pregnancy supplements after delivery and their UIC was rather low, their breast milk contained sufficient amount of iodine to cover the iodine requirements of the infant. This confirms the assumption that the mammary glands were able to concentrate iodine even in the face of maternal iodine deficiency (36).

A substantial number of women continued to smoke during pregnancy and lactation. While smoking and non-smoking breastfeeding mothers had similar levels concentrations of urinary iodine, breast milk of smoking

mothers contained substantially less iodine. Our results are consistent with thiocyanate inhibition of the NIS dependent route of iodine transport in the mammary glands. The insufficient transfer of iodine from mother to child exposes the breastfed infant to increased risk of iodine deficiency (37). Due to the biochemical characteristics of competitive inhibition, this effect could be reduced by higher iodine intake (38). According to one study, creatinine-standardised UIC can predict breast milk iodine concentration (39). However, it should be noted that smoking mothers were excluded from the analysis in that study (39). Our results clearly show that this correlation is valid only in non-smokers, and the UIC-based risk of iodine deficiency is underestimated in the infants of smoking breastfeeding mothers.

The main limitation of our study is that due to lack of power calculation, a type II error cannot be ruled out during comparisons of small subgroups. Furthermore, the cross-sectional study design prevented causality estimation. Generalisability concerns of the results may arise due to the high representation of under-educated women. Urinary iodine concentrations are influenced by both the time of spot urine collection and the time of the most recent iodine supplement intake prior to sampling (40); in our study, these parameters were not controlled or specified, and their influence on UIC may have led to misinterpretation in relation to the efficacy of iodine supplementation. Finally, no thyroid function tests were performed, and the sampling during pregnancy was timed after the first trimester, which is a less vulnerable period regarding iodine deficiency.

In summary, our findings strongly support that educational status is a major determinant of iodine nutrition during pregnancy and lactation in a rural area of Hungary. Higher educational status is associated with higher iodine intake and lower number of smokers. There was an expected association between maternal age and educational status since most births occur at age-appropriate education level. Higher educational status has been linked to higher income, higher socioeconomic status, and access to better health care and nutrition (41, 42). Furthermore, higher iodine intake may be an indicator of better diet quality (43). In areas where iodine fortification programmes are efficient, socioeconomic status does not influence iodine supply (44). In regions where natural diet does not cover iodine requirements and a national intervention programme has not been implemented, iodine supplementation depends on the knowledge and awareness of iodine (45).

In conclusion, we have shown that inadequate iodine supply in pregnancy and lactation is present in a Hungarian rural area. Both low iodine intake and smoking contribute to the higher risk of iodine deficiency in women with lower educational status. In breastfeeding mothers who continue to smoke, MIC is often low in spite of normal UIC; normal UIC may be misinterpreted as sufficient iodine supply towards the child. Antenatal health promotion strategies should focus on the use of iodine supplementation and cessation of smoking, especially among less-educated women.

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