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ORIGINAL ARTICLE

Thyroid homeostasis in mother–child pairs in relation to maternal iodine status: the MISA study

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BACKGROUND/OBJECTIVES: Iodine deficiency during pregnancy may influence maternal and foetal thyroid function with the risk of causing neurocognitive and psychomotor deficits in the offspring. The objective of this study was to assess iodine status in pregnant women from Northern Norway and to investigate the influence of iodine status on maternal and infant thyroid function.
SUBJECTS/METHODS: Women from the Northern Norway Mother-and-Child contaminant Cohort Study (MISA) donated a blood and urine sample at three visits during their pregnancy and postpartum period (in second trimester, 3 days and 6 weeks after delivery. $N = 197$). Women were assigned to iodine status groups according to urine iodine concentrations (UICs) in second trimester and mixed effects linear models were used to investigate potential associations between iodine status and repeated measurements of thyroid-stimulating hormone (TSH), thyroid hormones (THs), TH-binding proteins and thyroid peroxidase antibodies. Associations between maternal iodine status and TSH in heel prick samples from the infants were investigated with linear regression.
RESULTS: Median UIC in second trimester was 84 μg/l (range 18–522) and 80% had UIC below recommended level (< 150 μg/l). Iodine-deficient women had higher concentrations of T3, FT3 and FT4 (estimated differences (confidence intervals) of 0.10 nmol/l (0.01, 0.17), 0.16 pmol/l (0.05, 0.26) and 0.45 pmol/l (0.10, 0.78), respectively) compared with iodine-sufficient women. The concentrations varied within normal reference ranges, but the majority of women with subclinical hypothyroidism were iodine deficient. Maternal iodine status did not influence infant TSH concentrations.
CONCLUSIONS: This study indicate iodine deficiency among pregnant women in Norway. Iodine status during pregnancy influences maternal thyroid homeostasis and is therefore a risk factor for foetal and infant development.

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INTRODUCTION

Iodine is an essential nutrient involved in synthesis of thyroid hormones (THs), triiodothyronine (T3) and thyroxine (T4). THs are important in early growth and development of organs, and control major metabolic processes in the human body.[1] Iodine deficiency affects the health of people at all ages, however, pregnant and breastfeeding women, foetuses and children are especially vulnerable groups.[2] Health outcomes depend on the severity of iodine deficiency, where severe deficiency results in symptomatic disorders (for example, goitre, hypothyroidism, cretinism and infertility) and increased risk of spontaneous abortion, infant mortality and mental retardation.[1] Still, mild iodine deficiency may cause asymptomatic maternal hypothyroidism causing neurocognitive and psychomotor deficits in the offspring.[3,4]

Humans acquire iodine from the diet and dietary supplements, and marine food and eggs are the foodstuffs naturally highest in iodine. In Norway, cow fodder has been fortified with iodine since the 1950s, making dairy products important sources.[5] In a state of metabolic equilibrium, the body maintains an adequate storage of iodine in the thyroid where 5–10% dietary iodine is absorbed, whereas $>90\%$ is eliminated by renal excretion. For the general adult population, adequate iodine intake is considered 150 μg/day,[6] whereas for pregnant and breastfeeding women, increased metabolic requirements result in elevated TH production and increase in iodine requirements, hence these women are advised to have intakes of above 250 μg/day.[6] Iodine status can be assessed by urinary iodide concentration (UIC) and is a widely used method in population surveys to assess iodine nutrition among pregnant and breastfeeding women. The World Health Organization (WHO) has defined a median UIC of between 150 and 250 μg/l in pregnant populations as sufficient where UIC of 150 μg/l is estimated to reflect an iodine intake of 250 μg/day.[1,6]

Populations in many developed countries, including Norway, are believed to be iodine sufficient, however, monitoring studies have recently indicated increasing prevalence of iodine deficiency.[5,7,8] Major changes in Norwegian dietary patterns over the last decades have been suggested as one explanation.[7] Iodine deficiency is the most important and preventable cause of developmental brain damage,[6] hence population monitoring of iodine concentrations is important for public recommendations to secure appropriate iodine status. Considering the potential harmful effects of low iodine levels in pregnant and breastfeeding women, this study aimed to assess iodine status during pregnancy in a population from Northern Norway and investigate the influence of iodine status on maternal and infant thyroid function.

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MATERIALS AND METHODS

Study participants and collection of blood and urine samples

The study population comprise a subset of mother and child pairs from the Northern Norway Mother-and-Child Contaminant Cohort Study (the MISA Study), which consists of 515 enroled pregnant women, recruited from May 2007 to June 2009.[9] A total of 197 women with no prior thyroid-related disease, and with complete data sets consisting of maternal urine concentrations of iodine and creatinine, serum concentrations of thyroid parameters, and their infant thyroid-stimulating hormone (TSH) concentrations, were included in the study. The mothers gave written consents and answered a detailed questionnaire about diet and lifestyle, and donated a blood and morning spot urine sample at three time points related to their pregnancy (around gestational week 18, 3 days and 6 weeks postpartum). The women were requested to fast before blood samplings. Blood samples of infants were collected 3 days after birth. Detailed information about the study sites, study group characteristics, ethical approvals, the food frequency questionnaire and the sample collection procedures have been reported elsewhere.[9–11]

Chemical analyses

Serum analyses of TSH, THs and TH-BPs. Concentrations of maternal TSH, free- and total-T3 and T4, TH-binding proteins (TH-BPs; for example, TBG, transthyretin and albumin), thyroxine-binding capacity and thyroid peroxidase antibodies (anti-TPO) in serum samples were determined at the University Hospital of North Norway. Analytical methods, instrumentation, analytical variation and method-specific reference ranges are presented in Supplementary Table S1. The laboratory is certified according to ISO 151810.[12] The Norwegian National Unit for New-born Screening at Oslo University Hospital tested the new-born blood for TSH. Blood spots were collected on S&S or Whatman 903 filter paper (GE Healthcare Bio-Sciences, PGH, PA, USA) and analysed using Autodelfia neonatal TSH kits (PerkinElmer, Waltham, MA, USA).

Determination of iodine and creatinine in urine. Morning spot urine was analysed for iodine and creatinine at the National Institute of Occupational Health in Oslo, Norway. To prevent laboratory acquired infections and to dissolve urine precipitates, urine samples were heated for 1 h at 80 °C and cooled to room temperature prior to measurement. In all, 100 µl of an internal standard solution (1 mg/l of ^{129}I) was added to 1 ml of urine and diluted to 5 ml with deionised water. The concentration of iodine was measured determining the ^{127}I stable isotope by an element 2 inductively coupled plasma sector field mass spectrometer (Thermo Electron, Bremen, Germany) calibrated with urine matrix-matched standard solutions. Creatinine in urine was determined by the Jaffé reaction[13] using a SFA-200 flow injection analyser (Burkard Scientific Ltd, Uxbridge, UK). Seronorm Trace Elements human urine quality control materials (Sero Ltd, Billingstad, Norway) were used for quality assurance and the measured values were on average within ± 5% of the recommended values provided by the producer.

Calculated intake of iodine from self-reported food frequency questionnaire data. Self-reported dietary intake the last 12 months before inclusion was converted from amount and frequency to daily intake in grams per day using a standardised measurement table for weight and portion size.[14] Dietary intake of iodine in micrograms per day were further calculated from the various foods using the Norwegian Food Composition Database 2006.[15]

Statistical analyses

Statistical analyses were performed using SPSS software, version 23 (IBM SPSS Inc., Chicago, IL, USA). A significance threshold of $P < 0.05$ was used and Spearman's rho was calculated for correlations. Mixed effects linear models were used to investigate associations between UIC and three repeated measurement of TSH and THs, where women were assigned to iodine status groups according to UIC in second trimester of pregnancy; here classified as, deficient (UIC ⩽ 99 µg/l), mildly deficient (UIC = 100–149 µg/l) and sufficient (UIC ⩾ 150 µg/l), or assigned to quartiles according to UIC (all UICs are normalised by creatinine unless otherwise stated). Separate models were built for five dependent variables; TSH, T3, T4, FT3 and FT4 assessed as both native and log10-transformed concentrations in all models. Iodine status groups or quartiles and covariates were included as fixed factors. Homogeneity of variables across groups, diagnostic plots of the residuals and potential influential points were evaluated. Finally, maternal iodine status and associations to infant TSH concentrations were investigated using linear regressions adjusting for covariates (for example, gestational length, birth weight and age at sampling) and nonparametric tests of the difference in infant TSH concentrations across the maternal iodine status (Kruskal–Wallis test).

RESULTS

Population characteristics

Population characteristics, including important covariates, are presented in Table 1. Variations in infant clinical variables and TSH concentrations (Table 2) were within what is considered normal variation in infant populations.[16]

Urinary iodine and creatinine concentrations

In the second trimester, 63% of the women had UIC ⩽ 99 µg/l, 17% had UIC between 100 and 149 µg/l, and 20% had UIC ⩾ 150 µg/l (Table 3). Median UIC (normalised by creatinine) in second trimester, 3 days and 6 weeks postpartum was 84, 39 and 41 µg/l, respectively. Concentrations of iodine, creatinine and iodine normalised by creatinine at three time points for the whole group are presented in Supplementary Table S2. Creatinine concentrations were within normal reference ranges[17] and variance in concentrations were similar for all three time points.

Concentrations of maternal TSH and THs

Serum concentrations of TSH and THs varied within the normal reference ranges for the respective hormones.[18] Concentrations of TSH and THs during pregnancy, 3 days and 6 weeks postpartum, according to maternal iodine status and UIC quartiles (classified by UIC in the second trimester) are provided in Supplementary Tables S3 and S4, respectively. The percentage of women with mildly elevated TSH (⩾ 3.4 mIU/l) were 7, 19 and 2% in second trimester, 3 days and 6 weeks postpartum, respectively, where the majority of these women (70, 68 and 100%) were iodine deficient (UIC ⩽ 99 µg/l) in the second trimester. Fifteen women were categorised as anti-TPO positive according to the reference range

Table 1. Population characteristics and included covariates ($N = 197$)

Variable	*Median (range)*
Age	32 (18, 43)
Children/parity	1 (0, 4)
Gestational week at visit 1	18 (10, 34)
Sampling time visit 2 (days after delivery)	3 (1, 13)
Sampling time visit 3 (weeks after delivery)	7 (3, 24)
Pre-pregnancy BMI (kg/m^2)	23 (18, 44)
BMI at visit 1 (kg/m^2)	25 (18, 43)
BMI at visit 2 (kg/m^2)	27 (18, 45)
BMI at visit 3 (kg/m^2)	24 (17, 40)
Education: (years in school)	16 (8, 20)
Intake of dairy products (g/day)[a]	220 (7, 850)
Intake of marine food (g/day)[b]	69 (10, 252)
Intake of eggs (g/day)	17 (0, 59)
Dietary intake of iodine[c]	72 (8, 222)
	Categories
Dietary supplements (vitamins/minerals)	Yes/no
Blood sampling season	Month of the year
Time of day for blood and urine sampling	Hours:Minutes
Alcohol during pregnancy	Yes/no
Smoking	Yes/no

Abbreviations: BMI, body mass index; FFQ, food frequency questionnaire. [a]Includes milk, yoghurt, cheese, ice-cream and porridge made on rice and milk. [b]Includes shellfish, fish spread, processed fish, roe, liver, crab, fatty fish, lean fish, whale and seal. [c]Daily intake of iodine according to dietary intakes reported in the FFQ.

Table 2. Infant characteristics, TSH concentrations, and study population-specific reference range of TSH ($n = 197$)

	Boys/girls	*Median (range)*	*Study pop ref range*[a]
Gender	102/95		
TSH (mIU/l)		1.10 (0.07, 6.20)	0.20, 3.90
Gestational length (days)		282 (236, 299)	
Age at blood sampling (h)		72 (48, 364)	-
Birth weight (g)		3595 (1330, 4930)	-
Head circumference (cm)		36 (27, 40)	-
Length (cm)		50 (41, 57)	-

Abbreviation: TSH, thyroid-stimulating hormone. [a]Study population reference range defined as the 2.5 percentile (lower range) and 97.5 percentile (upper range) for this infant population.

Table 3. Concentration of iodine and dietary intake of iodine according to iodine status during pregnancy

Variable	*Deficient* (N = *123*)	*Mildly deficient* (N = *34*)	*Sufficient* (N = *40*)
	UIC ⩽ 99 μg/l	*UIC = 100–149 μg/l*	*UIC ⩾ 150 μg/l*
	Median (range)	*Median (range)*	*Median (range)*
Urine Iodine (μg/g creatinine)	66.9 (18.3, 99.6)	117 (101, 149)	197 (152, 523)
Reported dietary intake of iodine (μg/day)[a]	63.5 (8.12, 171)	80.6 (25.0, 179)	111 (24.3, 222)

Abbreviation: UIC, urine iodine concentration. [a]Daily intake of iodine according to dietary intakes reported in the FFQ.

applied by the manufacturer. The prevalence of anti-TPO was 7% for iodine-deficient women, 9% for mildly deficient women (UIC = 100–149 μg/l) and 10% for sufficient women (UIC ⩾ 150 μg/l). The anti-TPO-positive women were included in presented results as they did not influence model estimates.

Dietary intake of iodine

The estimated median dietary iodine intake was 72 μg/day and was weakly correlated with UICs in second trimester, 3 days and 6 weeks after pregnancy (r ($N = 197$) = 0.34, 0.28, 0.19, respectively). Participants reporting intake of supplements containing iodine ($N = 36$, median 112 μg/l) had higher UIC in the second trimester compared with those who did not take supplements containing iodine ($N = 161$, median 82 μg/l) ($P < 0.05$, Mann–Whitney *U*-test).

Iodine status and the association with maternal and infant thyroid homeostasis

Results from mixed models using hormone concentrations are presented in Table 4 and model estimates from models including log-transformed concentrations were similar. Iodine-deficient women had consistently higher concentrations of T3 (4.2%), FT3 (3.6%) and FT4 (2.3%) compared with sufficient women. The corresponding percentages for mildly deficient women were for T3 (6.8%) and FT3 (4.0%) (Table 4). Iodine-deficient women also had 10 and 3.4% higher median TSH and T4 concentrations compared with iodine-sufficient women, respectively, but the differences were not statistical significant (results not presented). TH-BPs and thyroxine-binding capacity were not associated to iodine status, but associated to TSH and TH concentrations, and were appropriately adjusted for in mixed models (indicated in footnotes in Table 4). Repeating the mixed models analyses for iodine quartile groups, demonstrated that women in the lowest iodine quartile had statistical significantly higher concentrations of FT3, FT4 and TSH compared with women within the highest iodine quartile (Figure 1).

Maternal iodine status in second trimester was not associated to infant TSH levels according to linear regression analysis ($P = 0.1$) or Kruskal–Wallis test ($P = 0.2$), and neither maternal iodine status nor infant TSH was associated with birth outcomes like birth weight and gestational age.

Table 4. Mean differences ($\Delta\hat{Y}$) in thyroid hormones estimated in mixed effects model across sampling points and iodine status

Models[a]		*Model 1:*[b] *T3 nmol/l*		*Model 2:*[b] *FT3 pmol/l*		*Model 3:*[b] *FT4 pmol/l*	
Fixed factor							
Iodine status groups[c]	*N*	*Δ Ŷ*	*95% CI*	*Δ Ŷ*	*95% CI*	*Δ Ŷ*	*95% CI*
Sufficient	40	Ref	—	Ref	—	Ref	—
Mildly deficient	34	0.16	0.06, 0.26**	0.18	0.05, 0.32**	0.30	−0.08, 0.73
Deficient	123	0.10	0.01, 0.17*	0.16	0.05, 0.26**	0.45	0.10, 0.78**

Abbreviation: CI, confidence interval. The mean T3, FT3 and FT4 in the sufficient group was 2.32 nmol/l, 4.47 pmol/l and 13.2 pmol/l, respectively. *$P \leqslant 0.05$, **$P < 0.01$ denotes a significant change in concentrations compared with the reference group (pairwise comparison: Bonferroni correction). [a]Models are based on three measurements of thyroid hormones per subject and included a subject-specific random intercept. [b]Age, BMI and thyroxine-binding capacity were included as covariates (fixed effects variables) in the model. [c]Estimations express change for thyroid hormone concentrations across iodine status groups, with sufficient as the reference group.

DISCUSSION

Main findings

To our knowledge, this is the first study investigating maternal and infant thyroid function according to iodine status in a Norwegian population. Iodine status during pregnancy influenced maternal blood concentrations of TSH and THs during pregnancy and

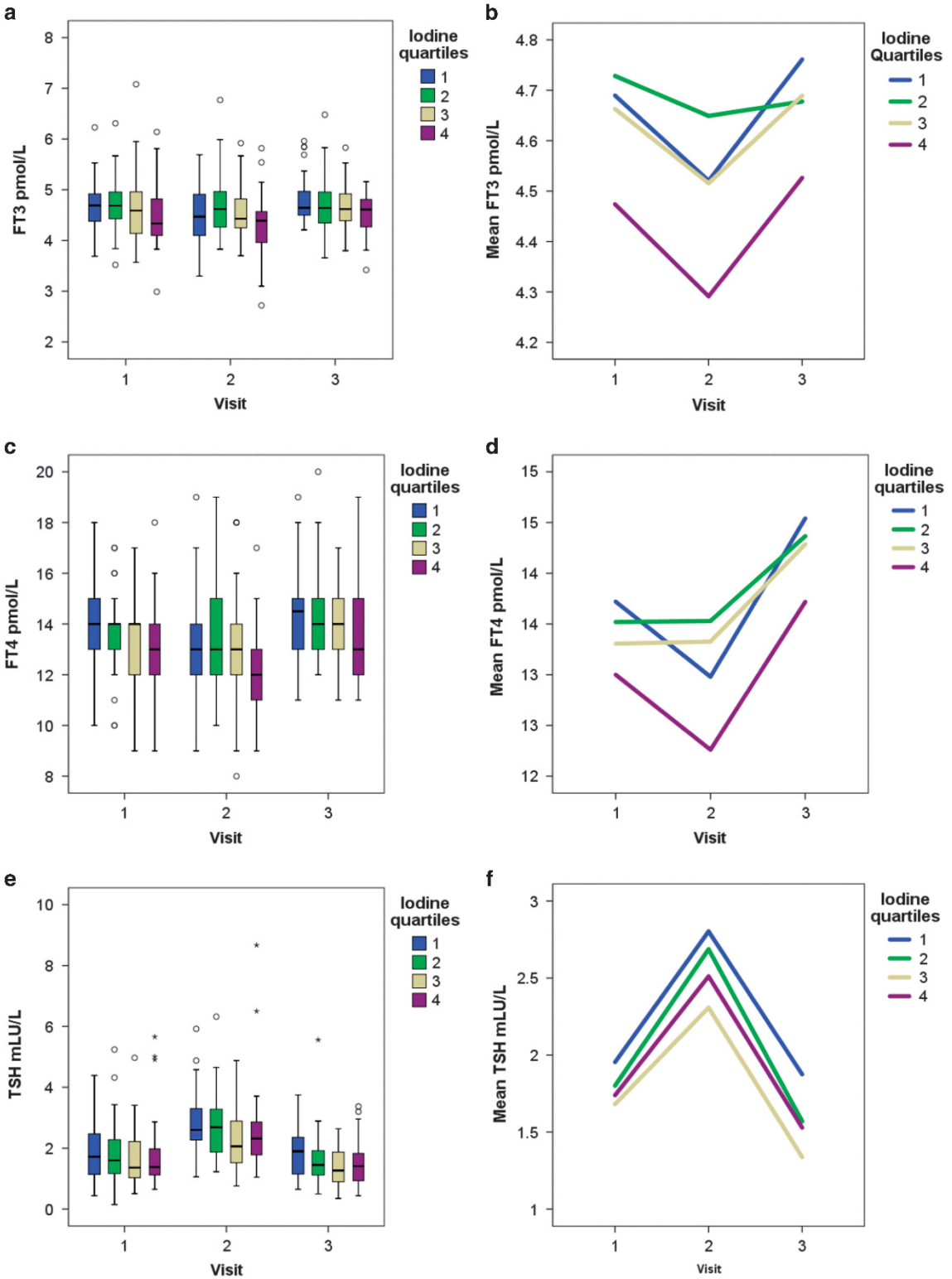

Figure 1. FT3, FT4 and TSH concentrations according to iodine quartiles at three time points, presented as mean concentrations (**a**, **c**, **e**) and as box plots (**b**, **d**, **f**). In the box plots, the width of the boxes represents sample size (quartile 1N = 50, quartile 2N = 52, quartile 3N = 49 and quartile 4N = 46).

postpartum periods. The population median UIC indicate an iodine-deficient population, and this observation support the suggestions of increasing prevalence of iodine deficiency that has been reported in many countries in Europe, including Norway.[8]

Iodine status during pregnancy

Eighty percent of the women had UIC below the recommended level for pregnant women in their second trimester. Comparable results were demonstrated in the 'Little in Norway' (LiN) study (*N* = 1036, year 2011–2012), where median UIC was 82 μg/l in

pregnant women and 80% of the women had UIC below recommended level.[19] Further, this is in accordance with iodine intake indicated by the self-reported dietary intake, where 94% women in this study reported an intake < 150 μg/day. Further, median dietary intake reported in the present study was considerably lower (72 μg/day) compared to that in women from the LiN study (153 μg/day). However, this may be explained by the difference in FFQs between our studies, and that dietary intakes were surveyed during pregnancy and included iodine supplements in more detail in the LiN study.

In this study, UICs likely reflect realistic iodine intakes over the last couple of days and probable increased dietary intakes of iodine because of elevated caloric intake during pregnancy compared with the food frequency questionnaires. Accordingly, if the daily iodine intakes in second trimester were estimated by extrapolation from UIC using the formula UIC (μg/l) × 0.0235 × body weight (kg),[1,20] iodine intakes are more comparable to the LiN study results (128 μg/day versus 153 μg/day in the LiN study). However, this extrapolation method assumes steady-state conditions (constant uptake and elimination of iodine), which is not likely for pregnant women and thus not a valid estimate in this population.

The low UICs in women reporting taking iodine supplements indicates that the amounts of iodine contained in supplements were less than what is required to optimise iodine intake for pregnant women. This is in accordance with two other studies, where women were iodine deficient despite reporting intake of iodine supplements.[21,22] This study results stress the need for evaluation of iodine status and potential general recommendations of iodine supplements for all pregnant women in Norway. Indeed, the Norwegian Council for Nutrition recently published an iodine status report, urging pregnant women to increase their dietary intake of iodine.[23]

Iodine status and association with maternal thyroid function

Women with UIC < 150 μg/l had consistently higher median concentration of TSH, T3, T4, FT3 and FT4 (TSH and T4 were not statistical significant) and were more likely to have subclinical hypothyroidism compared with women with UIC $\geqslant 150$ μg/l. This indicates a more hypothyroid profile in the iodine-deficient women where elevated TSH may have induced an increased production of THs. This is in line with a study of pregnant women,[24] where UICs (median of 103 μg/l) were inversely associated to FT3 and FT4 concentrations (the study did not include total-T3 and total-T4). Accordingly, if iodine intake is restricted during pregnancy, the pituitary thyroid feedback mechanisms could cause increased iodine uptake with stimulation of the thyroid and increased production of THs.[25] Further, depleted iodine stores in pregnant women have been associated with a negative iodine balance, which can result in elevated circulating TSH and an increased production of T3 instead of T4.[26] In this study, although T3 was higher in both deficient and mildly deficient women compared with sufficient women, there were no differences in T3/T4 ratio between the groups. Several studies report no associations between maternal UIC and thyroid function,[21,27,28] and in a study comparable to the present,[29] no associations between UIC and repeated measures of THs were found. However, that study population were classified as iodine sufficient (median UIC 160 μg/l in second trimester), hence, the influence on thyroid function by severity and timing of iodine deficiency vary between study populations and can explain discrepancies between study results.

In this study, TSH was statistical significantly different when comparing UIC quartiles, not when comparing iodine status groups. This may be realistic as previous reports demonstrate that in conditions of mild iodine deficiency, elevated TSH is typically demonstrated only in a small fraction of subjects,[26] which could have been better captured by the quartile analyses in this study. Indeed, the range in iodine deficiency within the deficient group ($N = 123$) were wider compared with in the lowest quartile ($N = 50$), which likely influenced the variance in TSH and subsequent statistical significance testing. Still, both approaches demonstrate the same overall results, which lends support to our interpretations of the results.

Maternal iodine status and infant thyroid function

We did not observe associations between maternal iodine status and concentrations of infant TSH. Indeed, there is little and conflicting evidence that TH homeostasis is impaired in the foetus of moderately iodine-deficient pregnant women.[27,30–32] However, maternal UICs were associated to changes in maternal thyroid homeostasis and foetal brain development in utero is probably more sensitive to changes in maternal THs compared with maternal iodine status. Still, iodine transfer through breastmilk is important for the new-born and adequate supply of iodine through breastmilk is critical for thyroid development, and thus, the low maternal UICs at 3 days and 6 weeks postpartum in this study may have implications for infant development.

Clinical relevance

Low UICs as reported in this study, do not necessarily indicate inadequate iodine supply for maintaining metabolic processes, but may reflect increased iodine trapping by the thyroid gland as its iodine uptake can be as high as 80%.[33,34] If iodine intake remains above a threshold of about 50 μg/day, increased uptakes of iodine could maintain adequate stores of iodine within the thyroid.[35] Accordingly, the indicated differences in TH concentrations because of iodine deficiency were within normal reference ranges for the respective hormones, and may not have caused clinical effects in the mothers. However, the foetus is dependent on maternal transfer of THs until birth and disruption of maternal TH homeostasis in any degree would only add to the challenges encountered by the new-born in meeting postnatal hormone requirements.[36]

Strength and limitations

UIC is recommended as a biomarker for iodine status.[37] Although UIC reflect recent intake, the iodine intake calculated from self-reported dietary habits referred to intake during the last year. The UIC was significantly correlated with dietary intake of iodine, however, self-reported iodine intake was much lower than the indicated daily intake according to UICs. Misreporting of dietary intake, missing iodine values in food consumption database and lack of information on use of iodised salts likely contributes to this difference, in addition to the different time periods covered.[37] Still, large individual variation in UICs has been reported, especially during pregnancy. To account for variation in dilutions of the spot urine, we normalised UIC according to creatinine. Further, the iodine status in second trimester were confirmed from UICs 3 days and 6 weeks postpartum Finally, UIC in morning urine is normally lower than in spot urine during the day,[35] however, it is the preferable measure as individual variance of iodine in morning urine is lower because of less influence from recent meals.[38]

Owing to the complexity of the thyroid system, assessment of potential thyroid impairment cannot be interpreted from individual TH levels only, and we included all major components of the thyroid system. As TH levels are influenced by physiological changes during pregnancy, we evaluated TH-BPs and thyroxine-binding capacity (reflects elevated levels of all the binding proteins) as a proxy in statistical models for the pregnancy-related alterations in blood.

CONCLUSIONS

This study indicates that the majority of pregnant women in Northern Norway are iodine deficient and intakes of iodine from diet are not adequate to reach recommended level. Iodine status

during pregnancy influences maternal thyroid homeostasis and is therefore a risk factor in foetal and infant development. Therefore, it is important to monitor iodine status in young adults and fertile women to prevent potential thyroid-related health effects in pregnant women and foetuses.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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