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Inter-relationship between evolutions of the temporal trend of urinary iodine excretion with iodized salt accessibility and thyroid function in an exclusive cohort of mothers residing in a mild iodine-deficient region

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Abstract

***Background & Aims*:** Maternal iodine deficiency (UIC<150 µg/L) is common in regions with borderline iodine sufficiency. Hence, exploring evolution of the temporal trend for UIC during pregnancy as well as impact of possible modifiers aids in defining the timing and the dose of iodide administration supplement during foetal development. The aim of present investigation was to evaluate the inter-relationships between UIC and iodized salt accessibility and thyroid function as assessed by thyroid-stimulating hormone (TSH) in an exclusive cohort of pregnant women depending on household salt as the predominant source of iodine intake.

Materials and Methods: Healthy pregnant women (n=95; gestation > 4 and < 8 weeks) and non-pregnant women (n=40) with similar lifestyle and dietary habits were enrolled. UIC, TSH and table-salt iodine content were determined.

Results: Median UIC (µg/L) according to trimesters was significantly lower than that of controls (61.6, 130.2 and 90.3 vs 133.8). Accordingly, prevalence of subjects with UIC<150 µg/L were 97.9, 67.4, 77.9 and 60. Median TSH (mIU/L) according to trimesters and control group were 1, 1.6, 1.4 and 1.6. Accordingly, prevalence of subjects with abnormal lower TSH limit was 17.2, 8.5, 3.2 and 2.4.

Conclusion: This investigation demonstrates that UIC varies according to the foetal life cycle and that the highest frequencies of severe iodine (UIC <50 µg/L) were identified at the first- and third trimesters. This investigation paves the way for future studies aiming at exploring the therapeutic impact of iodine supplementation on body iodine stores during pregnancy.

***Keywords*:** Thyroid stimulation hormone (TSH), urinary iodine excretion (UIC); Pregnancy; Iodine, Maternal iodine deficiency

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Introduction

Iodine is an essential trace element required for thyroid hormones biosynthesis. The most prevalent

consequences of iodine deficiency during early pregnancy are impaired motor and cognitive functions of the offspring (1) .

Nutritional iodine intake of a population is evaluated by median Urinary Iodine Concentration (UIC). According to the World Health Organization (WHO), a median UIC of ≥ 150 µg/L and ≤250 µg/L is considered desirable during pregnancy (2). Accumulating data have revealed that maternal iodine deficiency (UIC of < 150 µg/L) is more prevalent among women with adequate iodine intake than those with optimum- or more than iodine intake (3-11). National Health and Nutrition Examination Survey (NHANES; 2005-2010) has revealed that median UIC during pregnancy was 129 µg/L despite optimum iodine status in the United States. Interestingly, 57% of the studied population exhibited a UIC < 150 µg/L (12). UIC monitoring in European countries with sub-adequate nutritional iodine intake has revealed that about 58% of the pregnant women were burdened with various degree of ID (13). According to a study from Lyon (France) assessing UIC according to trimesters, global median was 81 µg/L (n=228; range: 8-832) (11). Prevalence of participants with UIC <150 µg/L, <100 µg/L and <50 µg/L) were 77%, 58% and 27%, respectively (11). A similarly designed study from Latvia reported that global median was 69.4 µg/L (n=829; range: 53.9-92.6) µg/L8. Distribution of subjects with UIC < 150 µg/L was 81% (8). Delshad and colleague have reported that moderate maternal iodine deficiency (UIC: 87.3 µg/L) is common in Iran despite of iodine sufficiency in school children (161 µg/L)(14). Despite the importance of maternal iodine sufficiency from clinical and public health point of views, limited information is available on the temporal trend of UIC during pregnancy and impact of possible modifiers in regions with adequate iodine intake (3, 4, 10, 11, 14).

This aims of the present study were to 1) evaluate accessibility adequately iodized salt during pregnancy; 2) explore evolution of the temporal trend for UIC and 3) examine the inter-relationships between iodine accessibility and thyroid function. To minimize the impacts of possible UIC modifiers including socioeconomic-, dietary-, geographic- and ethnic variations, a distinctive cohort of pregnant women relying on household salt as the predominant source of iodide intake was studied.

Materials and Methods:

Study design:

This cross-sectional study was performed in the mountainous region of Ziweh (Urmia, West Azerbaijan, Iran). The location is exclusively settled by native Kurds (15528 inhabitants; 419 annual births). Healthy pregnant women (n=107; age 26.4±5.0 years) were randomly enrolled from 11 primary local health offices. The participants were followed up at first-, second and third trimesters. Overall drop-out due to missing biochemical information or failure in completing the study was 11% (n=12). Inclusion criteria was all gravid women attending first prenatal check-up (gestational age >4 and <8 weeks based on the date of last menstrual period). Exclusion criteria were: 1) multiple pregnancies; 2) taking iodine and/or vitamin supplement; 3) previous history of thyroid diseases and/or history of drug affecting thyroid function; and 4) non-natives. Women of childbearing age residing were enrolled as the control group (n=40; Age: 25.7±4.6 years). Exclusion criteria for the women of childbearing were: non-natives; 2) taking iodine and/or vitamin supplements; 3) history of thyroid dysfunction. Food frequency questioner (FFQ) of the studied population is shown in Table 1.

Ethics Approval and Informed Consent:

This study was approved by the ethical committee at Urmia University of Medical Sciences, Urmia, Iran. Written and verbal consent were obtained from pregnant women and non-pregnant women.

Sample collection:

Table salt: Before the date for urinary sample collection at first-, second- and third trimesters, the participants were approached at home and asked to provide us with a table salt sample. The samples were transferred into dark-glass vials with lid and subsequently kept at -20ºC until analysis for iodine

content. In case non-pregnant women, the abovementioned approach was also employed

Urine: Random morning urine samples (10 mL) were collected in sterile plastic tubes. Aliquots (2 mL) were transferred to Eppendorf tubes and subsequently stored at -70 C° until analysis.

Whole blood: Venous blood (5 mL) was collected after 12 hours of fasting. Serum was separated according to routine laboratory protocol. Serum aliquots (1 mL) were transferred to Eppendorf tubes and were subsequently stored at -70°C until analysis.

Measurements:

UIC determination: The assay was performed using the Sandell–Kolthoff reaction as previously described elsewhere (15, 16). The Inter-assay and intra-assay for UIC determination were 2.1% and 3.3%.

TSH-assay: Serum TSH was determined using a third-generation immunochemiluminometric assay (DiaSorin, LIAISON® Analyzer).

Salt-iodine assay: The titration method for potassium iodate was used as described elsewhere (17). All the samples were analyzed in duplicate by one person. The Inter-assay and intra-assay were 3.1% and 4.3%.

Statistical analysis:

Data handling was carried using SPSS software for windows version 16 (IBM Inc., Chicago, USA). Quantitative data were expressed as either median or mean SD. Normality of data distribution was assessed with Kolmogorov–Smirnov test. Non-parametric data were analysed by the Mann–Whitney test. Differences between categories were tested with one-way ANOVA or Scheffe test for multiple comparisons. Spearmen s rho test used to assess the correlation between non-parametric items. Correlations between the different parameters were calculated by linear regression analysis. P≤0.05 was considered statistically significant.

Results

Mean age of pregnant subjects at entry was 26.4±5.0 years (range: 17-40 years; median: 26). The frequency of subjects <30 years and > 30 years were 76.8% (n=73) and 23.2 % (n=22). Mean BMI at entry into the study was 26±4.5 Kg/m2 (range: 15.8–39 Kg/m2). Distribution of individuals with BMI (< 25 and >25) were 50.5%% (n=48) and 49.5% (n=47). Mean age and BMI of non-pregnant women were 25.7±4.6 years (range: 18-37 years; median: 26) and 25.8±4.5 Kg/m2 (range: 18.3–43.5 Kg/m2). Distribution of non-pregnant women with BMI (< 25- and >25) were 52.5% (n=21) and 47.5% (n= 19).All the participants stated that no other sources of salt than the commercially iodized form were used for household purposes. Frequencies of salt samples with free- (0 ppm), inadequate- (1-14 ppm), adequate- (15-30 ppm) and excessive (≥30 ppm) iodine content according to trimesters and non-pregnant women are presented in Table 2.

Median UIC values at first- and third trimesters were lower than that of second trimester (61.6 µg/L and 90.3 µg/L vs 130.2 µg/L: P-Values: 0.001). The respective value for the control group was 133.8 µg/L. Mean ± SD, median, and 95th % reference range for pregnant women according to trimester and non-pregnant women are shown in Table 3.

We applied WHO criteria for Iodine Deficiency (ID) in our participants. ID criteria for non-pregnant women and schoolchildren was: <20 µg/L Sever ID, 20-49 µg/L Moderate ID, 50-99 µg/L Mild ID, 100–199 µg/L adequate, 200–299 more than adequate and >300 excessive, and For pregnant women ID criteria was:<50 µg/L Sever ID, 50-99 µg/L Moderate ID, 100-149 µg/L Mild ID, 150–249 µg/L adequate, 250–499 more than adequate and >500 excessive iodine intake (18).

Prevalence of participants with UIC <150 µg/L, 150 µg/L > and <249 µg/L or >250 µg/L according to trimesters of pregnancy were as follows: 97.9%, 2.1% and 0%; 67 %, 23.4% and 9.6%; 77.9%, 15.8% and 6.3%, respectively (Table 4). In the case of control group, prevalence of subjects with UIC <100 µg/L, 100 µg/L > and <199 µg/L, and >200 and >299 µg/L and >300 µg/L were 20%, 47.5%, 20% and 12.5% (Table 4).

Median TSH level at first trimester was 1 mU/L. This was lower than those of second- and third trimesters (1.6 mIU/L and 1.4 mIU/L; P<0.005 and P<0.05). Median TSH concentration for control group

was 1.6 mIU/L. Means ± SD, median and 95th % reference ranges for TSH during pregnancy and non-pregnant women are presented in Table 5. Comparison of reference ranges for TSH in the present study, the European Thyroid Association (ETA) guideline and the American Thyroid Association (ATA) is presented in Table 6.

Table 1: Assessment of food intake (food frequency questionnaire) of the participants

Items	Never or less than once a month	1-3 times a month	Once a week	2-4 times a week	More than 4 times per week
Poultry	21.2%	10.2%	16.5%	44.7%	7.4%
fish	64.6%	22.8%	6.9%	3.9%	1.8%
Meat	25%	18%	19%	31.5%	7.7%
Egg	23.5%	6.3%	18.8%	40.4%	11%
Bread	1.2%	---	---	---	97.8%
Grain	---	10%	20%	46.6%	23.4%
Yogurt	---	---	20%	38.3%	41.7%
Milk	---	30%	14.5%	21.5%	34%
Cheese	---	---	8.2%	5.9%	85.9%
Fruits	7.5%	39%	27.9%	13.9%	9.7%

Table 2: Iodine content in table-salt samples collected from pregnant women and non-pregnant controls

Participant	Iodine Free (< 0 ppm)	Low (1-14 ppm)	Adequate (15-30 ppm)	More than adequate (>30 ppm)
First trimester	8.2% (n=7)	11.8% (n=10)	60% (n=51)	20% (n=17)
Second trimester	11% (n=9)	11% (n=9)	59.8% (n=49)	18.3% (n=15)
Third trimester	9.2% (n=7)	7.9% (n=6)	60.5% (n=46)	22.4% (n=17)
Non-pregnant	8% (n=3)	5% (n=2)	74% (n=30)	13% (n=5)

Table 3: Median, mean and reference range (5^{th} – 95^{th}) for urinary iodine excretion (UIC; µg/L) for pregnant- and non-pregnant women

Participants	N	Mean±SD	Median	Reference Range
I*	95	61.4±39.2	61.6	10–119
II	95	144.1±71.8	130.2	39–290
III	95	105.8±73.8	90.3	13–254
Non-pregnant**	40	165.2±82.1	133.8	75–353

* Significant differences between second trimester and first- or third semester (P=0.001).

**Significant differences between non-pregnant women and first- or third semester (P=0.001).

Table 4: Classification of median urinary iodine excretion of participants according to WHO criteria for nutritional iodine status

	Severe ID	Moderate ID	Mild ID	Sufficient	More than adequate	Excessive iodine intake
1st semester	25.5±13.1 (n=38; 40%)	75.1±13.8 (n=47; 49.5%)	114.3±16.8 (n=8; 8.4%)	214.6±27.2 (n=2; 2.1%)	0%	0%
2nd semester	35.5±12.5 (n=9; 9.6%)	86.9±12.5 (n=12; 12.8%)	124.5±14.2 (n=42; 44.6%)	196.5±31.5 (n=22; 23.4%)	297.8±46.7 (n=9; 9.6%)	0%
3rd semester	28.6±12.9 (n=25; 26.3%)	86.2±12.4 (n=34; 35.8%)	117.8±11.5 (n=15; 15.8%)	194.7±28.7 (n=15; 15.8%)	286.4±48.9 (n=6; 6.3%)	0%
Non-pregnant women	------	-------	87.33±10.9 (n=8; 20%)	128.1±24.3 (n=19; 47.5%)	227.8±27.9 (n=8; 20%)	331.5±26.7 (n=5; 12.5%)

Table 5: Mean±SD, median and reference range (5th – 95th) for serum TSH in pregnant- and non-pregnant women.

	N	Mean ± SD	Median (IQR)	Min – Max	P5 – P95
1st semester	95	1.14±0.87	1.0 (0.53 – 1.47)	0.01 – 3.85	0.03 – 2.87
2nd semester	95	1.71±0.90	1.64 (1.09 –2.24)	0.02 – 3.98	0.29 – 3.53
3rd semester	95	1.52±0.74	1.41 (1.02 – 1.91)	0.02 – 3.44	0.42 – 3.0
Non-Pregnant Women	40	1.71±0.84	1.6 (1.12 – 2.24)	0.35 – 3.60	0.61 – 3.28

Table 6: Comparison of reference ranges for TSH in the present study, the European Thyroid Association (ETA) guideline and the American Thyroid Association (ATA) and other national and international studies

	1st semester	2nd semester	3rd semester	Non-pregnant women
ATA reference range	Up to 2.5	Up to 3	Up to 3	
ETA reference range	Up to 2.5	Up to 3	Up to 3.5	
This study reference range (P5-P95)	0.03 – 2.87	0.29 – 3.53	0.42 – 3.0	0.61 – 3.28

Discussion

Understanding the temporal trend for UIC during pregnancy aids in defining the timing and the dose of iodine supplement during foetal development in a population. Investigation in regions with optimum- or more than adequate iodine supply have shown no renal iodine changes during pregnancy suggesting whole body iodine meets the demand during maternity (19-21). On the other hand, conclusive data regarding the temporal trend for UIC in pregnant women residing in regions with moderate to adequate iodine sufficiency is limited. Two separate investigation from France and Latvia have reported that median UIC in the first trimester was slight lower than those of second- and third trimesters, respectively (8, 11) whilst a study from UK has reported a modest increase in UIC with advancing gestational age (3). The reason(s) for the discrepancy in UIC temporal trend with advancing gestation are not clearly understood.

In this study, we report that the temporal trend for UIC during pregnancy was bell-shaped with the highest iodine uptake occurring at the first trimester followed by

the third trimester. Our finding indicate that the high demand for iodide in early pregnancy. This is reflected by significant reduction in the magnitude of median UIC when compared to that of non-pregnant women. Moreover, a marginal but significant decline in UIC was also identified at the third trimester. Another important finding from this study is that UIC value at the second trimester was not different from that of no-pregnant women. This finding implies that thyroidal iodine uptake has been leveled down at the second trimester before commencing to rise at the third trimester. In the current investigation, evolution of the temporal trend for UIC overlaps with that of thyroid hormone biosynthesis during foetal life cycle reported elsewhere (22). Possible factors explanations for the bell-shaped trend of UIC with advancing gestational age in the present study are homogeneity of studied population, stable dietary habits, the reliance on table salt as the main source of iodine and clustering of urine sampling times. Indeed, other investigators have attempted to overcome the large intra-individual variations in UIC among urban populations by introducing measures such as repeated UIC, 24 hours iodine excretion but without a significant progress (23, 24). The cross-sectional nature of the project did not permit performing repeated UIC or 24 hours iodine excretion as confirmations.

Frequencies of pregnant women with UIC< 150 µg/L varied from 67.1% to 97.8% according to trimesters. In the first trimester percentage of pregnant women with UIC (150-249 µg/L) and those with UIC >250 µg/L were 2.1% and 0%, respectively. In the case of the third trimesters, the respective figures were 15.8% and 6.3%. These findings indicate that renal iodine clearance during pregnancy are determined by a range of factors including iodine transfer to the fetus, placental storage of iodine, changing renal physiology and intra-thyroidal iodine stores (25). In agreement with previous studies, we show that the current established criteria for iodine adequacy in populations of school age children (>100 µg/L) do not meet the need of pregnant women. The high prevalence (40%) of subjects with UIC <50 µg/L at the first trimester is of great concern as reduction in thyroid hormone production may be detrimental to the foetus and the mother. The results of this investigation pave the way for future studies aiming at exploring the therapeutic impact of iodine supplementation on body iodine stores during pregnancy.

Due to considerable variation in TSH reference intervals among different populations, health establishments have recommended that local references ranges should be established according to guidelines. Our study also reaffirms previous finding from different population that that alteration of TSH levels during pregnancy differ between the stages of gestation as well as between maternity and women of childbearing age (11). Although a higher percentage of the pregnant women in this study were iodine deficient (UIC <150 µg/L), no inter-relationships were seen between global TSH levels and UIC nor between trimester specific TSH levels and their respective UIC values. When the median for TSH in the first trimester was compared to that of the European Thyroid Association (ETA; median:1 mU/L, range: 0.1–3.8 mU/L), it was found that 82.8% (=77) fell within the same range for ETA whilst only 17.2% (n=17) exhibited values below the lower limit. In the case of second- and third trimesters, the figures were 85.1% (n=80) vs 8.5% (n=8) and 95.8% (n=91) vs 3.2% (n=3). The respective figures for non-pregnant women were 97.5% (n=39) and 2.5% (n=1). Interestingly, only the lower value for TSH in the first trimester was different from that for a cohort of Iranian pregnant women residing in urban areas (0.03 mIU/L vs 0.2 mIU/L) (10, 26). On the other hand, our trimester specific values for TSH were lower than those reported by Nazarpour et al. for a cohort residing in an iodine sufficient area (27). Taken together, these finding imply the demand for the establishment of local references for TSH in each province. .

Conclusion:

In conclusion, this investigation is the first to demonstrate that temporal trend for UIC in pregnant women residing in a border-line iodine sufficient region varies according to foetal life cycle. The highest trapping of dietary iodine occurred at the first trimester followed by the third trimester. The high prevalence

(40%) of pregnant women with (UIC <50 µg/L) at the first trimester is of great concern as reduction in thyroid hormone production may be detrimental to the foetus and the mother. These findings urge for tailored intervention strategies to minimize the adverse impact of maternal iodine deficiency on the mother and the offspring.

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Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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