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Urinary Iodine Concentration as an indicator of Iodine status and its Correlation with the Thyroid hormones and Hemoglobin levels in first trimester pregnant women - An Exploratory Study

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Abstract

During pregnancy, the daily requirement of iodine increases making those most at-risk population for iodine deficiency disorders. The available confined data shows that pregnant women are iodine deficient even in iodine sufficient regions with this background the objectives of the current study were to assess the urinary iodine concentration (UIC) and evaluate the relationship between the levels of hemoglobin, UIC, and thyroid status in first-trimester pregnant women. A cross-sectional hospital-based study with a total sample size of n=110 pregnant women at the13th week of gestation in the Mysuru district was selected. The UIC, anthropometric measurements, iodine intake, and selected biochemical parameters (TSH, FT3,FT4, and Hb) were assessed. The data was analysed using SPSS (v 16.0). Spearman's rank correlation test was used to analyse correlations. The Mann- Whitney U test was used to compare differences between groups. Kendall's tau b rank test was used to study the association of pregnancy complications with UIC and hemoglobin levels. The median UIC (mUIC) was 194.2 µg/L and Hb was 10.5 g/dL. Even though the mUIC was normal, around 38.2% had insufficient UIC. Significant inverse relationship between UIC and TSH ($r = -0.487$, $p<0.001$), Hb and TSH ($r = -0.355$, $p < 0.001$), and between TSH and iodine intake ($r=-0.476$, $p<0.001$) were observed. It was interesting to observe that those with insufficient UIC were found to have mild anaemia and low FT4 levels and those with excess UIC had lower TSH levels. The pregnant women in the present study were found to have the normal median urinary iodine concentration and were mildly anaemic. Increased attention among pregnant women should be focused on iodine status along with iron status and thyroid functions. Larger comparative studies need to be performed to study the impact of altered iodine status on neonatal outcomes.

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Introduction

Iodine, a micronutrient is obligatory for the production of thyroid hormone in humans.[1] Inadequate iodine intake may result in irreversible fetal brain damage and complications like stillbirth, increased number of spontaneous abortions, attention-deficit syndrome, hearing defect in infants, impaired psychomotor growth, behavioral disorders, and congenital anomalies. Pregnancy is also known to be related to an increase in requirements of thyroid hormone, due to the physiological alterations resulting from the transfer of thyroid hormone and iodine to the fetus.[2] On the other hand, excessive intake of iodine can alter thyroid function. Studies have reported an increase in the prevalence of subclinical hypothyroidism, overthypothyroidism, hyperthyroidism[3] and autoimmune thyroiditis.[4] Since most of the iodine consumed is expelled in the urine, urinary iodine (UI) is an excellent biomarker of recent iodine intake and spot urine samples that are easy to obtain and are relatively cost-effective is the best indicator for assessing the iodine status of the population. Although daily or even within the same day the variations in an individual's urinary iodine concentration (UIC) are observed, these variations tend to attenuate within populations, providing a useful measure of the iodine status of populations.[5] Anemia, a worldwide health problem affects around 33% of non-pregnant women and 38% of pregnant women. Low concentrations of hemoglobin and anaemia are important risk factors for health and development. During pregnancy, it may be associated with an increased risk of maternal and perinatal mortality and low weight and size at birth. Iron deficiency is the most common cause of anaemia and is highly prevalent in developing countries like India. Also, maternal and neonatal deaths are a major cause of mortality.[6] Deficiency of iron with or without anemia affects the development of the child and may also have numerous adverse effects on thyroid metabolism by reducing the activity of heme-dependent thyroperoxidase in the thyroid and may blunt the effectiveness of iodine prophylaxis.[7] Also, studies have shown that deficiency of iron is related to thyroid function and may lead to hypothyroidism during early pregnancy.[8,9] Adverse pregnancy outcomes were associated with UIC < 50 µg/L and also the prevalence of thyroid dysfunction was higher in this group.[10]

In Europe, in the early 1980s, it was confirmed that the presence of continued iodine deficiency affected neonatal thyroid function and therefore a threat to early brain development.[11] Furthermore there is limited recent data among pregnant women to assess the progress of the National Iodine Deficiency Disorders Control Programme of India, which recommends resurveys amongst the vulnerable population groups every five years.[12]

The current cross-sectional study was planned to assess the UIC and evaluate the relationship between hemoglobin levels, UIC, and thyroid status in first-trimester pregnant women which is less explored in southern India, Karnataka.

Material and Methods

Subjects and data collection

A total of 110 healthy pregnant women were recruited from the three maternity hospitals in Mysuru district, with the inclusion criteria of women to be healthy pregnant with a single fetus in good physical condition aged 18–40 years in the 13th week of gestation. The exclusion criteria included subjects who had a personal history of thyroid disease; subjects who took thyroid-related medicine; pregnant women who had some other metabolic disorders and those not willing to participate. The present study was conducted in Mysuru district of Karnataka, Southern India, and was piloted from January to December 2019 based on convenient sampling.

The study protocol was approved by Institutional Human Ethics Committee (IHEC-UOM NO. 156/ Ph.D/2017-18).

Informed consent was obtained from the pregnant women who were willing to participate in the study. Data was collected at the hospitals, using a questionnaire to elicit information on demographic parameters. Spot urine samples were collected for determining UIC and 3 ml of venous blood was collected for analyzing thyroid-stimulating hormone (TSH), FT3 and FT4 levels, by a technician.

Laboratory Analysis:Testing Samples of spot urine were obtained from every participant and stored at -20°C until analysis. The excretion of Urinary iodine was measured using an ammonium persulphate method based on the Sandell-Kolthoff reaction.[13] Hemoglobin was measured using Mission Hemoglobin Testing System (San Diego, USA). 3 ml of venous blood sample was collected and subjected to centrifugation at 3000 rpm for 5 minutes for serum separation. Analysis of TSH, FT3, and FT4 was done using an immunometric assay with Abbott architect i1000sr plus system analyzer (Ireland). Reference ranges from the manufacturer were used. Before testing, calibration of all assays and quality control limits for each was established and completed. Quality control samples were tested and specimen testing only continued when controls were within limits. The reference ranges for TSH levels <0.24 μIU/mL is considered as low, 0.24-4.17 μIU/mL as normal and >4.17 μIU/mL as high, for FT3 levels <1.49 pg/mL is considered as low, 1.49-4.55 pg/mL as normal, >4.55 pg/mL as high and for FT4 levels <0.93ng/dL is considered as low, 0.93-1.51ng/dL as normal, and >1.51ng/dL as high.[14]

The reference range of UIC in pregnant women are less than 150 μg/L is considered as iodine insufficient, between 150-249 μg/L as adequate, between 250-499 μg/L above requirement and more than 500 μg/L as iodine excess.[15]

A semi-structured questionnaire was developed by the authors to collect information regarding basic demographic information such as name, age, contact method,previous pregnancy-related complications, and present symptoms. The socio-economic status was analyzed using theKuppuswamy scale.[16] Anthropometric measurements, height, and weight were measured according to the standard anthropometric techniques.[17] Using height and weight measurements, Body Mass Index (BMI) (kg/m^2) was calculated. By using the formula, the daily iodine intake was calculated - Daily iodine intake (μg/day) = UIC (μg/L) x 0.0235 x body weight (kg).[18]

Data analysis: All statistical analyses were completed using the SPSS v16.0 software. The Shapiro – Wilk test was used to test data distribution normality. The data were described using median and percentile values. UIC, TSH, FT4, FT3, Hb, and iodine intake were used to analyze the relationship between them, to estimate the correlation analyses Spearman's rank correlation test was used and Kendall's tau b rank test was used to study the association of pregnancy complications with UIC and hemoglobin levels. The difference between the adequate, inadequate and excess UIC group were compared using the nonparametric tests were conducted (Mann-Whitney U test and Kruskal-Wallis H test). When the 2-tailed p-value was <0.05 the results were considered statistically significant.

Results

Characteristics of pregnant women: The average age of the pregnant women was 23.9 ± 3.9 years. The media values of UIC, TSH, FT3, and FT4 were found to be adequate and normal respectively in the study population. Though the levels of FT4 were within the normal range it was towards the lower side (Table 1). The mean Hb values were found to be 10.5g/dL indicating the pregnant women to be mildly anaemic.

Table 1: General characteristics, urinary iodine concentration, thyroid function test and median daily iodine intake of pregnant women in southern India

Parameters	Pregnant women (n=110)
Age(years)[a]	23.87 ± 3.909
BMI(Kg/m2)[a]	24.06 ± 4.895
Laboratory tests	
mUIC (μg/L)[b]	194.20 (30-817.98)
TSH (μIU/mL)[b]	1.61 (0.15-10.64)
FT3 (pg/mL)[b]	2.910 (1.41-4.26)
FT4 (ng/dL)[b]	0.97 (0.68-1.51)
Hb (g/dL)[a]	10.5 ± 1.305
MeanDaily iodine intake (μg/L)	303.72 (42.3-870.94)

[a]Means ± SD. [b]Median (interquartile range). mUIC-median urinary iodine concentration, BMI-Body mass index; TSH- Thyroid-stimulating hormone, FT3- free Triiodothyronine, FT4- free thyroxine, Hb: hemoglobin.

Frequencies and percentage of pregnant women in different levels: The frequency and percent of pregnant women falling in different categories revealed most of our study population belonged to the upper-lower and lower-middlesocio-economic group. The majority (38.2%) of the study population had insufficient UIC and around 30.9% and 7.3% had UIC more than adequate and excess respectively. Around 13.6% of the study population had TSH levels high (>4.17) whereas 30% of FT4 had low levels. About 22.7% and 20% of pregnant women were mild and moderately anaemic, respectively. The subjects reported about the previous pregnancy complications included abortion (11.8%), miscarriage (2.7%), and preterm delivery (12.7%). Around 33% of the pregnant women reported lethargy as a common symptom. (Table 2).

Table 2: Descriptive characteristics of the study population. (n=110)

Variables	F (%)
Socio economic status	
<5 (Lower)	Nil
5-10 (Upper Lower)	66 (60)
11-15 (lower middle)	27 (24.5)
16-25 (Upper middle)	13 (11.8)
26-29 (Upper)	4 (3.6)
Body Mass Index	
<18 (Underweight)	16 (14.5)
18-24.9 (Normal)	40 (36.4)
25-30 (Overweight)	41 (37.3)
>30 (Obese)	13 (11.8)
Urinary Iodine Concentration (µg/L)	
<150 (Insufficient)	42 (38.2)
150-249 (Adequate)	26 (23.6)
250-499 (Above requirements)	34 (30.9)
>500 (Excess)	8 (7.3)
Thyroid Stimulating Hormone (µIU/mL)	
<0.24 (Low)	3 (2.7)
0.24-4.17 (Normal)	92 (83.6)
>4.17 (High)	15 (13.6)
Free Triiodothyronine (pg/mL)	
<1.49 (Low)	1 (0.9)
1.49-4.55 (Normal)	109 (99.1)
>4.55 (High)	Nil
Free Thyroxine (ng/dL)	
<0.932 (Low)	33 (30.0)
0.932-1.51 (Normal)	77 (70.0)
>1.51 (High)	Nil
Hemoglobin (g/dL)	
>11 (Non-anemic)	63 (57.3)
10-10.9 (Mild anemic)	25 (22.7)
7-9.9 (Moderately anemic)	22 (20.0)
<7 (Severe anemic)	Nil
Previous Pregnancy Complications	
Abortion (yes)	13 (11.8)
(No)	97 (88.2)
Miscarriage (yes)	3 (2.7)
(No)	107 (97.3)
Preterm-delivery (yes)	14 (12.7)
(No)	96 (87.3)
Present Pregnancy symptoms	
Lethargy (Yes)	36 (32.7)
(No)	74 (67.3)

Relationship between UIC, hemoglobin status, and thyroid function in the first trimester: The association of UIC, TSH, FT3, FT4, iodine intake, and Hb is as shown in Table 3. Spearman's correlation analysis showed a significant ($p < 0.001$) negative correlation between UIC and TSH and a significant ($p < 0.001$) positive correlation with FT3, FT4, Hb, and iodine intake. A similar trend was observed for Hb and daily iodine intake, but TSH was negatively correlated with UIC, FT3, FT4, Hb, and daily iodine intake.Based on the UIC level measured, we found that iodine intake levels were significantly ($p< 0.001$) different among the different subgroups of UIC. The iodine intake was significantly lower in the UIC < 150 µg/L group when compared with the UIC 150–249.9 µg/L group, UIC 250-499 µg/L and the UIC > 250 µg/L group (p=0.001). Also, a significant difference was observed in Hb levels in the insufficient UIC groups. Nosignificant difference for FT3, FT4, and TSH levels was observed among the groups (Table 4).

Table 3: Relationship between urinary iodine concentration, hemoglobin, thyroid function, and intake of iodine in first trimester pregnant women (n=110)

Variables	UIC (µg/L)	TSH (µIU/mL)	FT3 (pg/mL)	FT4 (ng/dL)	Hb (g/dL)	Daily iodine intake (µg/L)
UIC (µg/L)	1.000	-0.487**	0.287**	0.351**	0.712**	0.918**
TSH (µIU/mL)	-0.487**	1.000	-0.229**	-0.297**	-0.355**	-0.476**
Hb (g/dL)	0.712**	-0.355**	0.265**	0.414**	1.000	0.680**
Daily iodine intake (µg/L)	0.918**	-0.476**	0.222**	0.346**	0.680**	1.000

Spearman "rho" correlation coefficient: statistical significance. **$p < 0.01$. UIC-urinary iodine concentration; TSH- Thyroid-stimulating hormone, FT3- free Triiodothyronine, FT4- free thyroxine, Hb- hemoglobin.

Table 4: Levels of thyroid hormones, hemoglobin, and iodine intake in pregnant women among different urinary iodine concentration groups (n=110)

Group	N	TSH (µIU/mL)[a]	FT3 (pg/mL)	FT4 (ng/dL)	Hb (g/dL)[b]	Daily iodine intake (µg/L) [c]
UIC µg/L						
<150	42	3.89	2.72	0.932	9.95*	121.483*
		(0.21-10.64)	(1.41-3.48)	(0.68-1.45)	(7-11)	(42.30-263.582)
150-249	26	2.2	2.82	0.99	11.8	255.66
		(0.67-10.59)	(1.55-4.26)	(0.70-1.29)	(10.2-12)	(142.112-502.666)
250-499	34	1.135*	2.995	0.995	11.9	413.476*
		(0.15-6.37)	(1.99-4.2)	(0.70-1.29)	(8.4-13)	(250.260-861.045)
>500	8	0.83*	3.19	1.1	12*	763.954*
		(0.35-1.34)	(2.29-3.63)	(0.82-1.51)	(9-12.2)	(517.649-870.941)

The TSH, FT3, FT4, Hb levels, and iodine intake were expressed as median and interquartile range. Values of TSH, FT3, FT4, Hb, iodine intake and UIC levels were compared using Kruskal-Wallis H test with post hoc Mann-Whitney U test

a,b,cTSH, Hb and daily iodine intake levels were significantly different among different UIC groups ($P < 0.001$)

*Indicates significant difference when compared with adequate UIC group ($p< 0.01$).

A significant difference was observed for pregnancy complications like lethargy (p=0.001) associated with variations in UIC, also significant difference was observed for previous and present pregnancy complications like abortion, miscarriage, pre-term delivery, and lethargy (p<0.001 and p<0.002) associated with variation in Hb levels (Table 5).

Table 5: Association between pregnancy complications and symptoms with UIC and Hb

Complications	UIC	Hb
	p-value*	p-value*
Abortion	0.000	0.004
Miscarriage	0.260	0.275
Pre-term delivery	0.000	0.001
Lethargy	0.000	0.000

*Kendall's tau-b correlation, the correlation is significant at 0.01 level.

Discussion

The median level of UI in the current study was 194.2 µg/L, suggesting that the population had adequate iodine nutrition, according to the recommended standard of WHO.[16] In our study the thyroid functions were normal. Though the value of FT4 was less (0.97 ng/dL) it was found to be within the normal range. In the first trimester, there is an increase in total T4 consequently due to an increase in levels of thyroxine-binding globulin (TBG) under the influence of increased estrogen concentration. Since these changes are very trivial, as observed in non-pregnant women most pregnant women's serum FT4 concentration remains within the normal range.Saha *et. al*. have reported that the levels of FT4 remained within normal range in iodine sufficient areas whereas in iodine deficient areas it decreased progressively.[19] Requirement of iron is greater during pregnancy and as pregnancy progresses, the requirements of iron will increase steadily as the weight of the fetus increases. If the iron supplementations are not initiated in the mothers, it may increase in severity of iron deficiency anaemia (IDA). The iron status of the pregnant women in the present study was an alarm indicating the study population to be mild anaemic at the beginning itself. Around 40% were having Hb levels between 7-10.9g/dl. With these low levels of Hb in the first trimester, the pregnant women are at risk of becoming more anaemic during later trimesters resulting in adverse pregnancy outcomes. The developed countries will have most women enter pregnancy with normal Hb levels whereas in developing countries, large numbers of women are anaemicprior to conception.[20] Our findings reflect a similar situation, mild and moderate anaemia was found in most of the subjects in the first trimester of pregnancy. Normal Hb values and good iron supply are protective against perinatal neonatal mortality and also to improve the hematologic status.[21]

The mUIC is a better indicator of population iodine status. Although the mUIC was within the normal range among the women in the current study, individual iodine status varied, as most of our study population had insufficient UI. Iodine deficiency is known to have a contrary effect on the development of the fetus, which necessitates improvement in iodine status during pregnancy.[4] Bath and his co-workers in the Avon Longitudinal Study of Parents and Children assessed the association between maternal iodine status and child IQ at age 88 years and reading ability at age 9 years. The authors found that children whose mothers had inadequate UIC levels in pregnancy had lower reading accuracy and IQ scores.[22] Higher mUIC than optimum observed in our study also indicates excessive iodine intake and raises concern about the risk for iodine-induced hyperthyroidism and may also induce hypothyroidism, especially in an individual with unknown Hashimoto thyroiditis.[23]

With the increase in UIC, there was a decrease in TSH levels. The reasons for the elevation of TSH in iodine deficiency are implicit.[24] Positive correlation was observed between UIC and serum FT3 and FT4. A similar correlation was observed by other researchers.[25] Serum TSH levels were strongly negatively correlated with FT3 and FT4 levels. Korevaar and co-workers showed the pregnancy outcomes were better correlated with FT4 than with total T4.[26] Further, the increased TSH levels and iodine intake were negatively correlated with reduced Hb levels. Our results were in agreement with the study done by Baghel *et. al*.[7] For the production and transformation of thyroid hormone metabolism, iodine and iron are very important and deficiency of these nutrients often coexist. Low levels of hemoglobin were significantly associated with thyroid dysfunction and anaemia.[27] The data on human trials have shown that deficiency of iron is accompanied by reduced serum T4 and T3 as compared with healthy controls.[28] Additionally, in adolescent Iranian girls with iodine sufficiency and iron deficiency, iron supplementation improved iodine efficacy by increasing thyroid hormone (TT4, TT3, FT4) levels in children with iron deficiency with goiter.[29] In the present study, we observed that pregnant women with lower Hb levels showed a trend towards higher TSH and lower FT3 and FT4 levels. Our results are consistent with the results observed by Jinyan Fu *et. al*.[30] In a current study as the daily iodine intake increased there was an increase in UIC, FT3, FT4, Hb, and decrease in TSH levels. The effects of excessive intake of iodine can decrease the response of the thyroid to TSH and at higher concentrations, it inhibits the thyroid hormone secretion, iodide uptake, and oxidation.[31] Iodine and iron deficiency anaemia, collectively may decrease thyroid hormone synthesis, as iron is an important component of the TPO enzyme. Iron deficiency may block the ability of the child to use iodide and the dietary iodine may be of no use if iron is not supplemented simultaneously.

Further, when the different subgroups of UIC were compared, we found a significant ($p<0.01$) difference in iodine intake and Hb levels for the low UIC group when compared with the adequate UIC group. Significant ($p<0.01$) increase in daily iodine intake was observed in pregnant women with UIC more than adequate and excess.

Previous pregnancy complications like abortion, preterm delivery and symptoms like lethargy were found to be significantly associated with Hb and UIC. Iron deficiency particularly during the first trimester may lead to high-risk pregnancies like premature birth, low birth weight, termination of pregnancy.[32] iron deficiency may exert some effect on thyroid metabolism by interacting with iodine, an unclear mechanism, leading to the impairment of thyroid metabolism by IDA and lower the transport of oxygen, similar to thyroid impairment of hypoxia and also modify the response to prophylactic iodine.[33]

Conclusion

In conclusion, our study presents data on the iodine and thyroid status along with the Hb levels in early pregnancy and also evaluated the associations of UIC with TSH, FT4, FT3 concentrations in the region. It was observed that low Hb levels resulted in higher TSH and lower FT4 concentrations in the first trimester. Significant positive correlation between UIC, Hb, FT3, FT4, and iodine intake and a negative correlation between UIC and TSH levels were observed. Also, a negative correlation between the TSH and FT3, FT4, Hb, daily iodine intake, and UIC was noted. Based on our findings, increased attention must be given to improve iodine nutritional status along with correction of iron deficiency during pregnancy. Thus, monitoring iodine and Hb status and educating the pregnant women on adequate intake is needed during pregnancy as it has a direct consequence on neonates. The limitations of the study include smaller sample size, due to financial constraints only TSH, FT3, and FT4 were measured as indicators of iodine nutrition during pregnancy. However, blood thyroglobulin is also one of the good indicators. Also, the daily iodine intake was calculated and not measured.

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Conflict of Interest

The authors do not have any conflict of interest.

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