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Iodine Deficiency to Iodine Excess: Have We Come Full Circle?

İyot Eksikliğinden İyot Fazlalığına; Çemberi Tamamladık mı?

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Abstract

Objective: Recent studies have demonstrated an increase in the prevalence of hypothyroidism among pregnant women. Since hypothyroidism during pregnancy may increase fetomaternal morbidity, it is imperative to study the reason underlying this condition. Therefore, the present study was aimed to assess the iodine status in pregnant women and its correlation with hypothyroidism. **Material and Methods:** The present study was designed as a cross-sectional study to detect thyroid dysfunction in pregnant women in a tertiary-care hospital setting. Detailed demographics and the medical and obstetric history of the included subjects were recorded, and their baseline serum thyrotropin (TSH) and urinary iodine levels were determined. The women diagnosed with hypothyroidism were subjected to reflex testing for thyroid peroxidase antibodies (TPOAb). **Results:** The Median Urinary Iodine concentration of the study population, determined using the spot urinary iodine concentration of 545 women, was 255µg/L, which was higher than the level recommended in the WHO Guidelines. Among the 33% women (n=180) detected to be hypothyroid (TSH level >2.5mIU/L in the 1st trimester or >3.0mIU/L in the 2nd or 3rd trimester), 32% women (n=67) were positive for TPOAb. The correlation between the TSH levels and the urinary iodine levels was not significant (p=0.688); a significant correlation was observed between the urinary iodine levels and positivity for TPOAb (p=0.047). **Conclusion:** The current iodine status among pregnant North Indian women indicates a trend toward Iodine excess, with a significant association with the high prevalence of thyroid autoimmunity in the study population.

Keywords: Hypothyroidism; autoimmune thyroiditis; pregnancy; iodine

Özet

Amaç: Son çalışmalar, gebelerdeki hipotiroidizm prevalansında bir artış olduğunu göstermiştir. Gebelikte hipotiroidizm fetomaternal morbiditeyi artırabileceğinden, bu durumun altında yatan nedeni araştırmak şarttır. Bu nedenle, bu çalışmada gebelerde iyot durumu ve hipotiroidizm ile ilişkisinin değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Bu çalışma, 3. basamak hastane ortamında gebelerdeki tiroid disfonksiyonunu saptamaya yönelik kesitsel bir çalışma olarak tasarlanmıştır. Çalışmaya alınanların ayrıntılı demografik özellikleri ve tıbbi ve obstetrik geçmişleri kaydedilmiş ve başlangıç serum tirotropin (TSH) seviyeleri ve idrar iyot seviyeleri belirlenmiştir. Hipotiroidizm teşhisi konan kadınlara, tiroid peroksidaz antikorları (TPOAb) için refleks testi uygulanmıştır. **Bulgular:** Çalışma popülasyonundaki 545 kadının, spot idrar iyot konsantrasyonu kullanılarak, belirlenen Medyan İdrar İyot konsantrasyonu 255µg/L idi ve bu Dünya Sağlık Örgütü Kılavuzları'nda önerilen seviyeden daha yüksekti. Hipotiroid (TSH seviyesi 1. trimesterde >2,5 mIU/L ya da 2. veya 3. trimesterde >3,0 mIU/L) olduğu tespit edilen 180 kadından (%33) 67'sinde (%32) TPOAb pozitifti. TSH seviyeleri ile idrar iyot seviyeleri arasındaki korelasyon anlamlı değildi (p=0,688); TPOAb pozitifliği ile idrar iyot seviyeleri arasında ise anlamlı bir korelasyon gözlendi (p=0,047). **Sonuç:** Kuzey Hindistanlı gebe kadınlar arasındaki mevcut iyot durumu, çalışma popülasyonundaki yüksek tiroid otoimmünite prevalansı ile anlamlı bir ilişki gösteren iyot fazlalığına doğru bir eğilim olduğunu göstermektedir.

Anahtar kelimeler: Hipotiroidizm; otoimmün tiroidit; gebelik; iyot

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Introduction

Hypothyroidism is a global health concern and currently the most common cause of preventable brain damage. Thyroid hormones are essential for the proper development and differentiation of all kinds of cells in the human body. Hypothyroidism during pregnancy is reported to be associated with increased fetal and maternal morbidity.

Hypothyroidism during pregnancy is caused mainly due to two reasons: autoimmune thyroiditis and iodine deficiency. Therefore, recognizing the issue, several nations worldwide have introduced salt iodization programs to handle the growing concern of hypothyroidism. India adopted the Universal Salt Iodization (USI) policy in 1984, and since then, the production of iodized salt has increased at a gradual pace. The initiative has now been renamed as the National Iodine Deficiency Disorders Control Program. Currently, according to certain Indian studies, the iodine levels in the Indian population have reached adequate levels, particularly among the children in the school-going age-group. However, the iodine status among pregnant women has emerged as a concern, as some recent studies have demonstrated an increase in the detection of hypothyroidism during pregnancy. Although increasing the daily intake of iodine in accordance with the WHO guidelines during pregnancy is recommended to prevent hypothyroidism, certain studies have associated excess iodine intake with suboptimal thyroid function (1,2).

A previous study conducted in our institute reported a 19.7% prevalence of hypothyroidism, considering 4.0mIU/L as the normal upper limit of the thyrotropin/thyroid-stimulating hormone (TSH) level (3). Moreover, the American Thyroid Association (ATA 2017) has recommended investigating pregnant women with TSH levels >2.5mIU/L for autoimmune thyroiditis, which is expected to increase the detection rates of subclinical hypothyroidism even further (4).

In this context, the present study was aimed to determine the iodine status among the hypothyroid pregnant women, by measuring the spot urinary iodine concentration (UIC) and the levels of anti-thyroid peroxidase antibody (TPOAb), in order to investigate the correlation of these two parameters with hypothyroidism.

Material and Methods

The present study was designed as a cross-sectional study and was conducted in the outpatient clinic of the Obstetrics and Gynecology Department in collaboration with the Department of Biochemistry in a tertiary-care health center. The existing data for the Indian sub-continent, where the overall prevalence of hypothyroidism among pregnant women is reported to be approximately 10%, was used for calculating the sample size for the study, which was determined to be 553 for a confidence level of 95% and a precision of 0.025. In order to compensate for the errors in sample collection, 617 pregnant women who visited the Gynecology outpatient clinic were recruited, irrespective of their past thyroid status, period of gestation, or booking status. Those unwilling to provide informed consent for participation in the study were excluded. The study was commenced after obtaining the research and ethical clearance from the institutional review committee. İn accordance with the Declaration of Helsinki.

Detailed demographics and medical and obstetric information were collected and analyzed to rule out any other possible causes of thyroid dysfunction. Patient history was recorded to ascertain the following aspects: pre-existing thyroid disease, including symptoms of hypo-or hyperthyroidism; thyroid surgery or radioactive iodine exposure; associated autoimmune disorders in self or family; menstrual history; a history of high-risk obstetric factors, such as early pregnancy loss, preterm birth, history of diabetes or preeclampsia in the present or previous pregnancies; a history of intrauterine growth restriction or fetal demise; and history of placental abruption. Demographic information included the area of residence (rural or urban), a detailed history of the type of salt consumed (iodized or non-iodized), and the time of addition of salt to food (during cooking or after cooking). The participants underwent a clinical examination, including the assessments for Body Mass Index (BMI) and goiter, and the findings were recorded in a pre-designed format. Blood samples for TSH and the urine samples for spot urinary iodine concentration (UIC) were collected at the first visit. The women with TSH levels >2.5mIU/L in

the 1st trimester and 3.0mIU/L in the 2nd and 3rd trimester were considered hypothyroid according to the study protocol and were subsequently investigated for TPOAb in accordance with the recommendations of the American Thyroid Association guidelines of 2011 (5). The asymptomatic women with TSH levels in the hypothyroid range below 10.0 mIU/L were considered to have subclinical hypothyroidism (SCH), while those with the TSH levels above 10.0 mIU/L were diagnosed as having overt hypothyroidism. The TSH and TPOAb levels were determined with the chemiluminescence technique using commercially available kits in the Advia Centaur XP analyzer system (Siemens Healthcare Diagnostics). The analytical sensitivities for TSH and TPO were 0.010 mIU/L and 28 IU/mL, respectively, and the intra-assay coefficients of variation for TSH and TPOAb were 5.2% and 5.6%, respectively. The laboratory reference range for TSH was 0.35-5.5 mIU/L. A value of >60 IU/mL was used as the threshold to differentiate between TPOAb-positive or TPOAb-negative subjects as recommended by the manufacturer. Urinary iodine measurements were performed using an assay based on the Sandell-Kolthoff reaction (wet digestion method). The pregnant women with UIC levels less than 150 µg/L were considered iodine deficient, those with levels between 150 and249 µg/L were considered iodine sufficient, the ones with levels between 250 and 499 µg/L were grouped considered having higher than adequate levels of iodine, and those with levels >500 µg/L were considered having excessive iodine as per the WHO 2013 guidelines (1). The primary objective of the present study was to assess the levels of Median Urinary Iodine (MUI) and its correlation with thyrotropin levels in pregnant women.

Statistical Analysis

The normality of the quantitative data was assessed using the Kolmogorov-Smirnov test of normality. The normally distributed continuous data were expressed as mean±standard deviation. Since the spot urinary iodine concentration demonstrated a wide range of diurnal variation, the Median Urinary Iodine (MUI) level was calculated for the study population as recommended by the WHO (1). Categorical data were expressed as numbers or percentages (%). Proportions were compared using Fisher's exact test or Chi-squared test. Mann-Whitney Test and Kruskal-Wallis Test were employed to study the significance of variation in the MUI levels with the different parameters. The relationship of the urinary iodine levels to the TSH levels, TPOAb levels, and the area of residence (rural versus urban) was studied using the multiple logistic regression analysis. The urinary iodine levels were categorized as adequate, or higher than adequate, considering an upper limit of 249 µg/L (1). The IBM SPSS Statistics software version 22 was employed for the analysis of observations. All the statistical tests were two-sided and were performed at a significance level of $p<0.05$.

Results

The present study provided complete data regarding the medical history and clinical examination of 604 pregnant women. According to a set of predefined criteria, 33.2% of the women (n=201) were determined to be hypothyroid. Amongst these, 3.8% (n=23) women had overt hypothyroidism - eleven (1.8%) of them were diagnosed with the condition during the current pregnancy, while the remaining 12 women (2%) were diagnosed with hypothyroidism prior to the current pregnancy. In the TPOAb test conducted in the 201 hypothyroid women, 38.7% of the women (n=77) tested positive. Higher rates of TPOAb positivity were observed in women with overt hypothyroidism compared to the women with SCH (87% versus 32%; p=0.03).

Unfortunately, there was a loss of certain samples during handling and storage, because of which the spot urinary iodine concentration (UIC) data of only 545 subjects are available and presented in the present report. The mean age in these subjects was 25.34±3.56 years, and 13.2% of the women (72 in 545) were aged above 30 years. The mean BMI was 22.84±2.46 kg/m^2, with seven of the women (1.3%) having a BMI of >30 kg/m^2. The trimester-wise distribution of the enrolled women was 67.7% (n=369), 28.6% (n=156), and 3.7% (n=20) in the 1st, 2nd, and 3rd trimesters, respectively. The spot urinary iodine levels in the study popu-

Table 1. Distribution of spot urinary iodine levels in 545 women according to the WHO Guidelines (percentages presented in brackets).

Urinary Iodine Concentration (UIC)	Number of women (%)
Inadequate <150 µg/L	180 (33.0%)
Adequate 150-249 µg/L	91 (16.7%)
More than adequate 250-µg/L 499	203 (37.2%)
Excessive ≥500 µg/L	71 (13.1%)

lation ranged from 0-500 µg/L and the MUI was 255 µg/L, which is higher than the adequate levels according to the WHO standards (1). Table 1 presents the distribution of the spot urinary iodine levels in these 545 women.

Bivariate analysis was conducted to analyze the relationship of the MUI levels with the area of residence (rural versus urban), iodization status of the salt utilized, differences in the cooking practices, TSH levels of the study participants, and the TPOAb levels of the hypothyroid women, and the results are presented in Table 2. As visible in Table 2, the MUI level of the pregnant women living in rural areas was 235 µg/L, which was significantly lower (p=0.018) compared to those living in the urban areas (275 µg/L). While 92.5% of the women (n=504) were using iodized salt, 7.5% women (n=41) used rock salt in their households, and their MUI levels were 232.5 µg/L and 255 µg/L, respectively, which were not be significantly different (p=0.86). Furthermore, the data were analyzed to determine the effect of the time of addition of salt on the MUI level, and it was observed that the MUI level in the 525 women who preferred to add salt while cooking was 247.5 µg/L, while it was 292.5 µg/L for the 20 women who added salt at the completion of cooking. Again, this difference was not significant (p=0.460), probably because of the skewed distribution and the small sample size. In addition, no significant correlation was observed between the MUI levels and the serum TSH levels (p=0.68). The MUI levels in the euthyroid and hypothyroid women were 257.41µg/L and 239.47µg/L, respectively.

However, a significant correlation was observed between urinary iodine status and thyroid autoimmunity. The MUI level for the women with positive TPOAb was 255 µg/L, compared to the value of 195 µg/L for the women who were negative for TPOAb (Table 2), and this difference was statistically significant (p=0.047).

Similarly, the results of multiple logistic regression revealed a significant correlation of the MUI levels with the area of residence (p=0.036; odds ratio=1.798; CI=1.195-2.687) and the TPOAb levels (p=0.039; odds ratio=1.75; CI=1.029-2.978). The data is presented in Table 3.

Discussion

Hypothyroidism during pregnancy is reported to be associated with fetomaternal complications (4-6). While most of these complications are associated with overt hypothyroidism, the impact of SCH during

Table 2. Variations in median urinary iodine levels (MUI) in different subgroups.

Variables	Number of women (%)	Median Urinary Iodine (µg/L)	25th Percentile	75th Percentile	p value
Rural residence	256 (47%)	235.00	83.75	385.00	p=0.02
Urban residence	289 (53%)	275.00	125.00	421.50	
Euthyroid*	365 (67%)	255.00	111.25	420.00	p=0.68
Hypothyroid**	180 (33%)	245.00	82.50	390.00	
TPOAb Negative#	113 (63%)$	195.00	47.50	360.00	p=0.047
TPOAb Positive##	67 (37%)$	255.00	120.00	435.00	

*Euthyroid: ≤2.5 (mIU/L) in 1st trimester; ≤3.0 (mIU/L) in 2nd and 3rd trimester
**Hypothyroid: >2.5 (mIU/L) in 1st trimester; > 3.0 (mIU/L) in 2nd and 3rd trimester
#Thyroid Peroxidase antibody (TPOAb) negative ≤60 IU/mL
##Thyroid Peroxidase antibody (TPOAb) positive >60 IU/mL
$Thyroid Peroxidase antibody levels were tested only for hypothyroid women (n=180) as per the study protocol

Table 3. Relationship of the median urinary iodine levels to the TSH and TPOAb levels.

	p-value	Odds ratio	95% CI for Odds ratio	
			Lower	Upper
Area of residence (rural/urban)	0.036	1.798	1.195	2.687
TSH levels (euthyroid/hypothyroid)	0.497	1.338	0.578	3.095
TPOAb (positive/negative)	0.039	1.750	1.029	2.978

pregnancy remains unclear (7). However, SCH in the presence of autoimmune thyroiditis has been associated with early pregnancy loss and hypothyroidism in newborns in certain studies (8-10). This is a matter of concern as the literature reports a high incidence of autoimmune thyroiditis in women with SCH (11,12). In the present study, 32% of the women with SCH were positive for TPOAb. Moreover, accumulating evidence suggests that excess iodine levels are associated with autoimmune thyroid disease (13). Liu et al. have suggested the mechanism through which excess iodine levels may lead to the destruction of thyroid follicular cells (14).

Recently, scholars have questioned the practice of the routine supplementation of iodine during pregnancy in areas with mild-to-moderate iodine deficiency. In a systematic review published by Dineva et al, it was concluded that there is insufficient evidence to document both the safety and the significant positive impact of iodine supplementation during pregnancy on the cognitive development of the offspring (15).

The results of the present study revealed a significant correlation between excess urinary iodine and thyroid autoimmunity (p=0.047). Although there was poor correlation between the urinary iodine and the TSH levels (p=0.69), the hypothyroid women positive for autoimmune thyroiditis (TPOAb level >60 U/L) had significantly higher MUI (255 µg/L) compared to the women who were negative for TPOAb (MUI=195 µg/L). Similar to these findings, Shan et al. also reported that after 16 years of mandatory universal salt iodization in China, the prevalence of clinical and subclinical hypothyroidism and thyroid antibody positivity was significantly higher in the areas where people had more than adequate iodine intake (16). Evidence suggests that increased exposure to environmental iodine along with poor monitoring is the cause of this increase in the occurrence of autoimmune thyroid disease (17-20).

The MUI level of 255µg/L observed in the present study reflects that the iodine levels in our study population were higher than those recommended by the WHO. Over 50% of the women presented with UIC in the 'more than adequate' or 'excessive' range (1). Similar results were reported by Grewal et al. in the study population of pregnant North Indian women, with MUI=304 µg/L and over 78% of the study population presenting with UIC in the 'more than adequate' range (21).

Further data analysis in the present study revealed that the MUI level in the rural population was 235 µg/L compared to the value of 275 µg/L in the urban population, with the difference being statistically significant (p=0.02). However, no significant difference was observed in the MUI level between the women consuming iodized salt and those who consumed non-iodized salt. The higher MUI observed in our study population, particularly in the urban population, could be attributed to the higher consumption of salt in the urban areas. In the Salt and Mexico (SALMEX) cohort study conducted by Vega et al., MUI was reported to be significantly higher in the cohorts with higher salt intake, leading the authors to conclude that iodine intake is directly proportional to salt intake when both these parameters are adjusted to caloric intake (22). In another study conducted by Asvini et al., the mean daily salt intake estimates for nine different populations ranged from 6.9 g/day to 42.3 g/day, and the authors observed that the average salt intake in all these populations was greater than the recommended daily allowance of <5 g/day, with the greatest prevalence of high salt intake observed in urban India (23). In another study

conducted by Dhanwal et al, a higher prevalence of hypothyroidism was observed in the North Indian states compared to the states in South India, with the highest prevalence of 39% reported for Kashmir. This difference could be due to the ethnic variation or the difference in dietary patterns and, consequently, salt consumption (11).

In a recent study based on 24-h dietary recall surveys, Johnson et al. reported that salt intake in India is approximately 11 g per day, which exceeds the recommended intake of 5 g per day according to the WHO guidelines. The salt added to food at the time of processing/cooking was determined as a major contributor to salt intake. Higher salt intake in urban slums compared to rural areas was documented. The authors concluded that urgent action in terms of changing the consumer behavior is necessary to achieve the WHO's salt reduction target of 30% by 2025 (24).

The analysis of the effect of varied cooking practices and the time of addition of salt while cooking the food conducted in the present study revealed no significant differences in the MUI (p=0.57). This was contrary to the findings reported by Rana et al, who observed that iodine loss depends on the method of cooking and the time of addition of salt during cooking, with the losses during boiling, roasting, deep-frying, and microwave cooking determined to be 40.23%, 10.57%, 10.40%, and 27.13%, respectively, in their study (25).

The most significant findings of the present study are - the higher than adequate MUI of the study population and, at the same time, a high prevalence of SCH and autoimmune thyroid disease with a positive correlation between these parameters. Previous studies have also reported that autoimmune thyroiditis incidentally detected during pregnancy could be associated with an increased risk of recurrent miscarriage, postpartum thyroiditis, and chronic hypothyroidism. Therefore, it is imperative to monitor the thyroid health of pregnant women. The success of the universal salt immunization adopted by India in 1984 is reflected in the 4th National Family Health Survey (2015-2016), according to which 96.5% of the urban and 91.4% of the rural households are consuming iodized salt (26). However, the amount of salt being consumed and the environmental exposure to iodine should be monitored and regulated. In addition, it is important to educate the masses, such as through social media, regarding the harmful effects of excess salt consumption that could increase morbidity in terms of thyroid disease and also lead to several other chronic diseases such as hypertension.

Implications For Policy & Practice

The current iodine status among pregnant North Indian women indicates a state of iodine excess rather than iodine deficiency and is significantly associated with a high prevalence of autoimmune thyroiditis resulting in subclinical hypothyroidism, which in turn increases the risk of fetal and maternal complications. While the achievements of the National Iodine Deficiency Diseases Program must not be negated by questioning the necessity for the iodization of common salt, it is nonetheless imperative to monitor and regulate the iodine levels in table salt and increase the awareness among people regarding the harmful effects of excessive salt consumption.

Future Research Direction

High Median Urinary Iodine levels of our population are suggestive of excess intake of iodine through iodized salt. While we need to study dietary patterns and amount of salt consumption, there is probably a need to regulate the iodization levels of salt further.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and

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Authorship Contributions

Idea/Concept: Bharti Goel; Design: Bharti goel, Jasbinder Kaur, Poonam Goel; Control/Supervision: Bharti Goel, Jasbinder Kaur, Seema Gupta; Data Collection and/or Processing: Bharti Goel, Seema Gupta; Analysis and/or Interpretation: Bharti Goel; Literature Review: Bharti goel, Manjeet Kaur; Writing the Article: Bharti Goel; Critical Review: Mandeep Singla, Manjeet Kaur; References and Fundings: Government Medical College and Hospital, Department of Science and Technology.

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