High prevalence of iodine deficiency in pregnant women living in adequate iodine area

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Abstract

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Introduction

Iodine status is a global health concern, particularly in developing countries, and emphasis should be placed on diagnosis and correction at the community level rather than the individual due to the high impact in child neurological development and pregnancy outcomes (1, 2).

During pregnancy, daily iodine requirement increases by nearly 50% because of an increase in renal iodine excretion, increased thyroid hormone production and foetal iodine requirements (3). In iodine-sufficient areas, pregnant women maintain stable total body iodine levels throughout pregnancy. However, in mild-to-moderate iodine-deficient areas, total body iodine stores decline gradually from the first to the third trimester of pregnancy, and the potential changes in the mother's thyroid function during pregnancy are uncertain (4).

The recommended method to evaluate iodine nutrition status in a community of pregnant women is by measuring the urinary iodine concentration (UIC), thyroid size and serum thyroglobulin (sTg) (5). The UIC is most often used, but it indicates current iodine nutrition while thyroid size and sTg concentrations reflect iodine nutrition over a period of months or years. Measurements of UIC in randomly collected urine samples have proven to be useful, and consequently, iodine nutrition is defined as mildly-to-moderately iodine-deficient groups of pregnant women whose median UICs are between 50 and 150 µg/L (5). The median UIC values for United States pregnant women was 129 µg/L, which is consistent with a mild iodine deficiency (6). The American Thyroid Association (ATA) recommends that women who are planning to become pregnant or who are pregnant should supplement their diets with 150 µg/day of iodine (3).

Thyroid size is a sensitive marker for severe iodine deficiency because a goitre can be easily assessed by a physical examination and by a thyroid ultrasound. During pregnancy, the thyroids of mothers in iodine-deficient (moderate to low) areas will

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increase in size due to autoregulatory mechanisms of iodine on thyroid growth ([7](#)). There are limited data from pregnant women living in iodine-sufficient areas.

sTg also is a sensitive marker of iodine status as it reflects thyroid activity and hyperplasia ([8](#)). In iodine-deficient infants and children, the sTg concentrations are high, more often than are the serum TSH concentrations ([9](#)). Therefore, the sTg levels should be a good indicator of iodine nutrition in the general population and also in pregnant women ([10](#)).

Since 1953, salt iodization has been mandatory in Brazil, which is now reported to be an iodine-intake-adequate area with median UIC 276 µg/L, which was previously categorized as 'more than adequate' category (http://www.ign.org). However, iodine deficiency is still observed in a significant proportion of schoolchildren, especially from poor and uneducated families and rural regions ([11](#)). Previous small studies carried out in Brazil demonstrated an insufficient iodine intake in pregnant women, alerting about the adequacy of the iodine supply in Brazil, especially regarding the new determinations of the Brazilian government that recently reduced the concentrations of iodine in table salt to 15–45 mg/kg of salt ([12](#)).

We conducted this study to evaluate iodine status according to the median UIC, sTg and thyroid volume (TV) by ultrasound and thyroid function in pregnant women living in iodine-adequate areas during the three trimesters of pregnancy.

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Materials and methods

This cross-sectional study included 312 pregnant women who were consecutively recruited from the University Hospital Obstetric Outpatient Clinic and from the Einstein programme at Paraisopolis Community, both located in Sao Paulo (Sao Paulo State, Brazil) between April 2012 and June 2016. The exclusion criteria were ages less than 18 years, twin pregnancies, high-risk pregnancies (kidney disorders, hypertension, diabetes and HIV-positive), preeclampsia and known thyroid disease. Women taking iodine-containing supplements and thyroxine or drugs that interfere with thyroid function (amiodarone, glucocorticoid, lithium, biotin, metformin) also were excluded from the study.

The first analysis excluded pregnant women with thyroperoxidase antibody-positive and/or thyroglobulin antibody (TgAb)-positive measured by electrochemiluminescence immunoassays (ECLIA) methods (Roche Diagnostics, Mannheim, Germany and Beckman Coulter, Fullerton, USA). Pregnant women with TSH > 10 mIU/L were also excluded. The remaining 273 pregnant women were analyzed according to thyroid function, sTg, ultrasound examination of thyroid gland and UIC at each trimester.

The study was approved by the Institutional Ethical Committee of our Institution (Hospital das Clinicas HCFMUSP, CAPPesq nº 01503912.8.0000.0068). Written consent was obtained from all participants.

Biochemical and hormonal measurements

TSH, total and free T3 (TT3 and fT3), total and free T4 (TT4 and fT4), sTg and UIC were measured in all pregnant women. Blood and urine samples were collected between 08:00 and 10:00 h and were maintained at −20°C until measurement. The ECLIA were used to measure serum thyroid hormones (Roche Diagnostics, Mannheim, Germany and Beckman Coulter, Fullerton, USA), and all samples were measured in duplicate.

According to the manufacturer, the reference values for the non-pregnant population were 0.27–4.20 mIU/L for TSH; 1.3–3.1 nmol/L for TT3; 3.1–6.8 pmol/L for fT3; 66–181 nmol/L for TT4 and 12.0–22.0 pmol/L for fT4.

Spot morning urine samples (10 mL) were collected after overnight fasting from all participants in universal containers and transferred to Monovette tubes for transport and storage at −20°C until analysis. The adapted Sandell–Kolthoff reaction was used to determine the UIC, and all samples were measured in duplicate (13).

Thyroid ultrasonography

A thyroid ultrasound was performed on each pregnant woman by the same physician (Ana Carolina de Castro Nassif Gomes Monteiro) using a 7.5–12 MHz linear probe with a colour Doppler ultrasound programme (Philips IU-22, USA). Volumes of each thyroid lobe were calculated according to the rotation ellipsoid model: total TV (mL) = right lobe volume + left lobe volume + isthmus volume, considering depth (cm) × width (cm) × length (cm) × π/6 for each lobe. The thyroid echogenicity was characterized as normal or hypoechoic in comparison to cervical muscle echogenicity.

Statistical analysis

Data were analysed using IBM SPSS statistics for windows (Version 22.0.) and Minitab 17 statistical software (Version 2010; State College, PA, USA). Results were expressed as mean ± S.D. The normality tests used were Kolmogorov–Smirnov or Shapiro–Wilk. Comparisons between the numerical variables were performed by Student's t-test and one-way ANOVA while non-normal distribution was performed using Mann–Whitney and Kruskal–Wallis tests. The Bonferroni *post hoc*-test was applied to adjust for multiple comparisons. A P value of less than 0.05 was considered statistically significant.

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Results

A total of 273 pregnant women were evaluated, with mean ages of 28.1 ± 6.5 years, mean BMI of 26.2 ± 4.9 kg/m^2, and 40% were primigravida. Clinical characteristics of the study population according to each trimester of pregnancy are shown in Table 1.

Table 1

Demographic characteristics of the pregnant women in each trimester.

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Parameter	Trimester			
	First (*n* = 79) (<13th week)	Second (*n* = 108) (13–27th week)	Third (*n* = 86) (≥27th week)	
Age (years)	27.7 ± 6.5	28.5 ± 6.6	28.0 ± 6.5	*P* = 0.738
BMI (kg/m^2)	25.2 ± 4.8	25.8 ± 4.9	27.8 ± 4.7	*P* < 0.001
Median UIC (µg/L)	135	155	140	*P* = 0.132
Min–Max	69–285	27–403	41–316	
25th–75th	107–180	117–204	104–184	
% < 150 µg/L	53%	47%	58%	
TSH (mIU/L)	1.50 ± 0.92	2.03 ± 1.03	1.91 ± 0.96	*P* = 0.001
TT3 (nmol/L)	2.55 ± 0.43	2.94 ± 0.49	2.96 ± 0.52	*P* < 0.001

Parameter	First (*n* = 79) (<13th week)	Second (*n* = 108) (13–27th week)	Third (*n* = 86) (≥27th week)	
	Trimester			
TT4 (nmol/L)	144 ± 25.3	152 ± 34.0	146 ± 29.3	*P* = 0.350
fT3 (pmol/L)	4.59 ± 0.64	4.37 ± 0.52	4.14 ± 0.56	*P* < 0.001
fT4 (pmol/L)	15.6 ± 1.8	13.3 ± 2.1	12.5 ± 1.6	*P* < 0.001
sTg (µg/L)	13.9 ± 14.9	14.5 ± 14.0	12.8 ± 8.7	*P* = 0.701
TV (mL)	9.1 ± 4.2	9.2 ± 3.2	9.5 ± 2.9	*P* = 0.213

P value <0.05 was considered statistically significant.

*P values for the comparison between first and second trimester and first and third trimester.

sTg, serum thyroglobulin; TV, thyroid volume; UIC, urinary iodine concentration.

The median UIC of all pregnant women was 144 µg/L (range 27.3–403), which is indicative of iodine deficiency according to the World Health Organization (WHO) criteria for pregnant women (5). A UIC of <150 µg/L was found in 52% of the women, and a UIC of <50 µg/L was found in only 2%. Adequate iodine status (150–249 µg/L) was observed in 44% of the women, and only 4% had a UIC of ≥250 µg/L. The UIC showed no statistic differences among the trimesters of pregnancy, also considering percentiles 25th and 75th. Iodine deficiency status was more frequent in the third trimester, but the lowest median UIC was found in the first trimester (135 µg/L).

The mean TSH values were 1.50 ± 0.92, 2.03 ± 1.03 and 1.91 ± 0.96 mIU/L, in the first, second and third trimesters, respectively (*P* = 0.001 for all trimesters). The fT4 and fT3 values decreased significantly during pregnancy (*P* < 0.001 for all trimesters) (Table 1).

The TT4 and TT3 concentrations were higher during pregnancy. The TT4 concentrations remained stable throughout pregnancy, but the TT3 concentrations increased during consecutive trimesters, which was 29% higher than the reference values for the non-pregnant population.

The sTg levels did not change significantly during the trimesters (13.9 ± 14.9, 14.5 ± 14.0 and 12.8 ± 8.7 ng/mL, respectively). The median sTg was 11.2 ng/mL, and sTg above 40 ng/mL was found in only 3.3% of studied patients.

The mean TV was 9.3 ± 3.4 mL, and only 4.5% had TV exceeding 15 mL. The TV did not differ during pregnancy and positively correlated with the BMI (r = 0.319, P < 0.001) (Fig. 1), but not with the sTg and TSH. We found no correlation between TV and UIC. A thyroid nodule was detected in 19% of all pregnant patients.
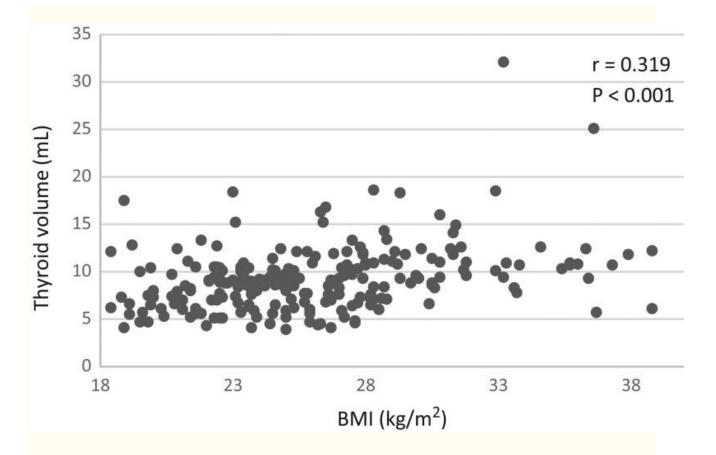

Figure 1

Relationship between body BMI and TV in pregnant women from an adequate iodine area. TV, thyroid volume.

When pregnant women were categorized as iodine deficient (UIC < 150 µg/L), iodine adequate (UIC ≥ 150 and <250 µg/L) and iodine excessive (UIC ≥ 250 µg/L), concentrations of sTg, thyroid hormones and TV at each trimester had no statistical difference according to the iodine status groups (Table 2).

Table 2

Thyroid parameters according to iodine status in the pregnant women.

	Iodine status		First			Second			Third	
		N	Mean ± s.d.	*P*	*N*	Mean ± s.d.	*P*	*N*	Mean ± s.d.	*P*
TT3 (nmol/L)	Deficiency	42	2.60 ± 0.42	0.360	51	3.04 ± 0.48	0.077	50	2.89 ± 0.54	0.408
	Adequate	36	2.51 ± 0.44		49	2.83 ± 0.46		32	2.99 ± 0.50	
TT4 (nmol/L)	Deficiency	42	148 ± 26.8	0.402	51	156 ± 33.4	0.432	49	140 ± 20.3	0.075
	Adequate	36	141 ± 23.4		49	149 ± 35.7		32	151 ± 34.6	
fT3 (pmol/L)	Deficiency	42	4.62 ± 0.59	0.760	51	4.31 ± 0.55	0.696	50	4.15 ± 0.57	0.898
	Adequate	36	4.49 ± 0.68		49	4.23 ± 0.49		32	4.15 ± 0.58	
fT4 (pmol/L)	Deficiency	42	15.6 ± 1.7	0.999	51	13.4 ± 2.2	0.586	49	12.3 ± 1.5	0.552
	Adequate	36	15.6 ± 1.8		49	13.2 ± 2.1		32	12.7 ± 1.7	

	Iodine status	First			Second			Third		
		N	Mean ± S.D.	P	N	Mean ± S.D.	P	N	Mean ± S.D.	P
TSH (mIU/L)	Deficiency	42	1.63 ± 0.95	0.376	51	2.27 ± 1.05	0.062	50	1.85 ± 0.91	0.154
	Adequate	36	1.34 ± 0.88		49	1.79 ± 1.01		32	1.95 ± 1.06	
sTg (µg/L)	Deficiency	42	14.7 ± 17.9	0.727	51	15.8 ± 17.0	0.597	50	12.5 ± 8.7	0.617
	Adequate	36	13.2 ± 10.8		48	13.4 ± 11.1		32	12.9 ± 8.6	
TV (mL)	Deficiency	38	8.5 ± 2.9	0.447	48	9.2 ± 2.7	0.946	43	9.4 ± 2.9	0.996
	Adequate	29	9.8 ± 5.4		45	9.2 ± 3.8		30	9.5 ± 2.8	

Values are expressed as mean ± S.D. N = number of pregnant women evaluated. Epidemiological criteria for assessing iodine nutrition in pregnant women according to World Health Organization (WHO): iodine deficiency UIC < 150 µg/L and iodine adequate UIC > 150 and <249 µg/L. P value for the comparison between iodine deficiency and adequate status in the trimesters. sTg, serum thyroglobulin; TV, thyroid volume; UIC, urinary iodine concentration.

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Discussion

In the present study, we support that iodine deficiency is frequent in pregnant women living in an area of adequate iodine consumption. According to WHO recommendation, in our cohort, iodine deficiency is considered mild, with a median of 144 µg/L. Several reports described iodine-deficient pregnant women even in iodine-sufficient areas,

(3, 12). In Brazil, the salt iodization programme is successful at combating iodine deficiency, but ongoing monitoring is mandatory as Brazil is a continental country with vulnerable regions, such as rural areas and lower economic conditions (11). Recently, the Brazilian government's salt iodization programme reduced the iodine concentration in salt from 40–60 mg/kg to 15–45 mg/kg based on previous reports pointing to excessive iodine intake (14). Our data were collected before the lower iodine concentration in salt was enacted, reinforcing the high risk of iodine deficiency in pregnant women in the next few years. Brazil also has no iodine supplementation programme for pregnant and lactating women as suggested in recent ATA guidelines, which recommend iodine-containing supplements (3, 12, 15).

Few reports analysed the UIC, thyroid function and TV with sTg in each trimesters of pregnancy. Thyroid hormonal findings here reflect the well-known physiological change: TSH increments, high levels of TT3 and TT4 and trend to lower fT4 and fT3 in the second and third trimesters of pregnancy. No differences in thyroid function were found according to iodine intake as previously described (10, 16).

The sTg is speculated to be a sensitive indicator of both low and excessive iodine intake (17). Zimmermann *et al.* suggested a median sTg of <13 µg/L and/or <3% of sTg values >40 µg/L indicates an iodine sufficiency in the population (18). Recently, Bath *et al.* performed sTg in pregnant women and found a negative association between iodine status (measured by the iodine-to-creatinine ratio) and sTg concentrations (10). The sTg was higher in the iodine-deficient group compared to the iodine-sufficient group, especially in later pregnancy. It is noteworthy that 15.7, 8.7 and 18.4% of women had a sTg > 40 µg/L in each trimester, independent of iodine status, and the median sTg was 21, 19 and 23 µg/L, respectively, in each trimester. In our study, the median sTg was 10.8, 11.3 and 11.2 µg/L, respectively, in each trimester, and only 3.3% of pregnant women had a sTg > 40 µg/L (3 patients in the first trimester, 5 in the second and 1 in the third). Therefore, sTg concentrations were not useful to determine iodine status in our cohort.

Thyroid enlargement also is an indicator of insufficient iodine intake, and 10–15% of pregnant women in areas with low iodine intake develop a goitre, besides the physiologic increment due to normal pregnancy (19). In the present study, we did not observe increments in TV during pregnancy or a higher frequency of goitres with no increment of sTg, probably because most women were mild iodine deficient so no differences in TSH concentrations were found. Although we found no difference in TV during pregnancy, TV was positively related with BMI, independent of the trimester. The effect of TSH on thyroid hyperplasia must be discreet since TSH levels remained in the normal range, and BMI was not correlated with iodine status and TSH. Our data indicate that a higher BMI increases TV mostly due to extracellular fluid expansion and blood volume increments that occur during normal pregnancy (20).

In the present paper, a 97% TSH concentration was 4.21 mIU/L, similar to previously described iodine-sufficient pregnant populations, and our frequency of subclinical hypothyroidism was 3.6% when considering a TSH of <4 mIU/L (3).

Our study had several limitations, as a dietary intake of iodine survey was not performed as well as the limited number of pregnant women evaluated in each trimester. Although the median UIC is a well-known indicator of iodine intake for the population, individual intakes are highly variable, and a low UIC on any given day might be found despite adequate daily intakes to maintain thyroidal iodine stores (21). Our study did not evaluate the socioeconomic and educational statuses that are associated with iodine deficiency (11).

Caution in accepting the necessity of iodine supplementation has been expressed, especially in areas where iodized salt is already in use (22). However, our findings reinforce a worldwide concern about the adequacy of the iodine intake of pregnant women. The iodine status evaluation in pregnant women must be reassessed with UIC, as it is the most appropriate method, in regular intervals to assess adequate intake and recommend supplementation if necessary. The Brazilian salt iodization programme prevents iodine deficiency but does not maintain iodine status within an adequate and recommended range for pregnant women, and ongoing vigilance is mandatory after the recent reduction of iodine in table salt (12).

In conclusion, iodine deficiency was found in 52% of pregnant women living in iodine-adequate areas. The sTg concentration and TV were not feasible to use as iodine status markers.

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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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