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Iodine nutrition, function, and volume of the thyroid gland in healthy pregnant women

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ABSTRACT

Introduction: Iodine deficiency during pregnancy damages maternal-fetal health. **Purpose:** The purpose of this study was to evaluate urinary iodine concentrations (UICs) in healthy pregnant women from the Plaza Municipality at different stages of pregnancy, trying to correlate such levels with thyroid function parameters as well as with thyroid volume. **Patients and Methods:** This cross-sectional study included 101 pregnant women from Plaza Municipality, in La Habana, Cuba, from September 2015 to August 2016. The variables analyzed were maternal and gestational age, trimester, skin color, number of children, smoking habit, UIC, thyrotropin, total and free thyroid hormones, thyroglobulin, and thyroid volume. The UIC was compared with the rest of the mentioned variables. **Results:** The UIC median in the total cohort was 153.5 μg/L (interquartile range 85.58-221.42) and 43.6% had values lower than 150 μg/L. In women with more advanced pregnancies, UIC was lower (first trimester 182.8 μg/L, second 160.2 μg/L, and third 143 μg/L). 91% of women with insufficient intake had a UIC between 50 and 149.9 μg/L. There were no statistically significant differences with clinical variables. Positive correlation of UIC with free T4 and T3 was demonstrated. Thyroid function parameters did not show statistically significant differences

RESUMEN

Introdución: La carencia de yodo durante el embarazo daña la salud materno-fetal. **Objetivo:** Evaluar la yoduria en embarazadas sanas del Municipio Plaza en diferentes etapas del embarazo y su relación con los parámetros de función y el volumen del tiroides. **Métodos:** estudio transversal que incluyó 101 embarazadas del municipio Plaza, La Habana, Cuba, desde septiembre de 2015 hasta agosto de 2016. Las variables analizadas fueron: edad materna y gestacional, trimestre, color de la piel, número de hijos, hábito de fumar, yoduria, tirotropina, hormonas tiroideas totales y libres, tiroglobulina y volumen tiroideo. La yoduria se comparó con el resto de las variables mencionadas. **Resultados:** la mediana de yoduria en la cohorte total fue de 153.5 μg /L (RIQ 85.58-221.42) y el 43.6% presentó valores inferiores a 150 μg/L. En mujeres con embarazos más avanzados la yoduria fue más baja (primer trimestre 182.8 μg/L, segundo 160.2 μg/L y tercero 143 μg/L). El 91% de las mujeres con ingesta insuficiente tenían una yoduria entre 50 y 149.9 μg/L. No hubo diferencias estadísticamente significativas con las variables clínicas. Se demostró la correlación positiva del yodo urinario con la T4 y T3 libres. Los parámetros de función tiroidea no mostraron diferencias estadísticamente significativas con los niveles de yodo. El volumen tiroideo medio fue

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according to iodine. The mean thyroid volume was 6.17 ± 1.7 mL and did not correlate with UIC. **Conclusions:** Iodine intake was adequate in the total cohort although bordering the lower limit and was insufficient in the third trimester. UIC was not related to clinical variables, thyroid function, or thyroid volume. (REV MEX ENDOCRINOL METAB NUTR. 2019;6:5-12)

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Key words: Pregnancy. Urinary iodine. Thyroid function. Thyroid volume.

de 6.17 ± 1.7 ml y no se correlacionó con la yoduria. **Conclusiones:** la ingesta de yodo fue adecuada en la cohorte total, aunque muy cercana al límite inferior, y resultó insuficiente en el tercer trimestre. La yoduria no se relacionó con variables clínicas, función tiroidea o volumen tiroideo.

Palabras clave: Embarazo. Yoduria. Función tiroidea. Volumen tiroideo.

INTRODUCTION

Iodine is an essential component of thyroid hormones, which play a pivotal role in cell metabolism and homeostasis, as well as in the growth and development of the fetus[1]. During the first trimester of pregnancy, both iodine and thyroxine (T4) readily cross the placenta, thus guaranteeing their proper supply to the developing fetal brain[2]. The synthesis of thyroxine-binding globulin (TBG) is increased during normal gestation, with its consequent increment in total thyroid hormone levels[3]. During the 1st week of pregnancy, chorionic gonadotropin (hCG) may increase thyroid hormone synthesis and secretion acting through the thyroid-stimulating hormone (TSH) receptor[4]. However, the high activity of placental Type 3 deiodinase results in an increased conversion and inactivation of T4 to rT3, thus preventing the excessive transfer of biologically active thyroid hormone to the fetus[5]. At the same time, the maternal renal clearance of iodine is also increased[3]. Pregnancy is known to be associated with an increased incidence of thyroid dysfunction and thyroid enlargement, particularly in women with iodine deficiency[6,7]. Taken together, all these gestational modifications of thyroid hormone physiology result in an increased requirement of iodine during pregnancy[1].

As a result of an official, Countrywide salt iodination program established in 2005, the incidence of goiter and thyroid dysfunction has sharply decreased in Cuba, particularly in children[8]. However, none of the vitamin supplements routinely prescribed to pregnant women in Cuba contains iodine. Although there are a few Cuban studies evaluating thyroid dysfunction during pregnancy[9], there are no published studies evaluating urinary iodine content and thyroid dysfunction in Cuban healthy pregnant women. The purpose of the present study was to evaluate urinary iodine content in women from the Plaza Municipality at different stages of pregnancy, trying to correlate such levels with thyroid function parameters as well as with thyroid volume.

PATIENTS AND METHODS

Patients

This is a cross-sectional study carried out between September 2015 and August 2016 in pregnant women living in the Plaza Municipality, an urban area nearby the sea in La Habana, Cuba. We excluded women with twin pregnancies and those with a personal history of thyroid disease. Participants were recruited by contacting the family medicine units of the area. In the same morning visit, demographic and clinical information (including a detailed obstetrics history) was obtained and blood and urine samples were collected. Thyroid ultrasonography was performed during the same visit as specified below. The protocol was approved by the scientific and ethics committees of the National Institute of Endocrinology and all participating subjects signed the corresponding informed consent.

Hormonal and biochemical measurements

TSH, total and free T4 and T3, thyroglobulin (Tg), as well as anti-Tg and antithyroid peroxidase (TPO) antibodies were determined using commercially available

kits from IZOTOP (Hungary). TSH was measured by means of an immunoradiometric assay with a functional sensitivity of 0.03 mIU/mL and inter- and intra-assay coefficients of variation (CVs) of 3.0% and 1.4%, respectively. Total T4 and T3 and free T4 and free T3 were measured by direct radioimmunoassay; for total T4, the functional sensitivity was 7 nmol/L and the inter- and intra-assay CVs were 2.8% and 2.3%, respectively; for total T3, the functional sensitivity was 0.3 nmol/L and the inter- and intra-assay CVs were 4.1% and 2.98%, respectively; for free T4, the functional sensitivity was 0.7 pmol/L and the inter- and intra-assay CVs were 2.83% and 0.94%, respectively; for free T3, the functional sensitivity was 0.58 pmol/L and the inter- and intra-assay CVs were 4.76% and 2.2%, respectively. Tg was measured by means of an immunoradiometric assay with a functional sensitivity of 0.1 ng/mL and inter- and intra-assay CVs of 1.7% and 1.8%, respectively. The manufacturer's reference ranges were 0.27-3.75 mIU/L for TSH, 50-170 nmol/L for total T4, 10-22 pmol/L for free T4, 1.5-3.4 nmol/L for total T3, 1.9-5.7 pmol/L for free T3, and 2-70 ng/mL for Tg. Anti-Tg and anti-TPO antibodies were measured by radioimmunoassay and were considered to be positive when higher than 100 mIU/mL. Urinary iodine was measured by the modified Sandell-Kolthoff method[10], as previously described.

Thyroid ultrasound

It performed with an Aloka SSD 1400 equipment (Mitaka-Shi, Tokyo, Japan), using a 7.5 MHz transducer. Thyroid volume was calculated using the Brun method (width × length × depth × π/6) as previously described[11].

Definitions

Normal TSH ranges were established according to the 2011 American Thyroid Association consensus guidelines as follows: first trimester 0.1-2.5 mIU/mL, second trimester 0.2-3 mIU/mL, and third trimester 0.3-3 mIU/mL[12]. The manufacturer's reference range for total T4 was multiplied by 1.5 in women of the second and third trimesters, as recommended by some authors[13,14]. A Tg level <13 ng/mL was considered normal and ≥13 ng/mL as indicative of iodine deficiency, based on previous researches[15-18], although there are no well-established cutoff points for Tg in pregnant women[19]. Iodine intake was classified according to urine levels as insufficient (<150 μg/L), adequate (150-249 μg/L), or excessive (250-499 μg/L). Iodine deficiency was further classified as mild (50-149 μg/L), moderate (20-49.9 μg/L), and severe (<20 μg/L)[20].

Statistics

Quantitative variables are expressed as means ± standard deviations when normally distributed and as medians with interquartile ranges (IQRs) when not. Qualitative variables are expressed as percentages. Differences in urine iodine excretion at different stages of pregnancy were analyzed by the Kruskal–Wallis test and their potential association with other clinical, demographic, ultrasonographic, and hormonal variables was explored using Pearson's correlation coefficient. Differences in hormonal measurements were evaluated using χ^2, Student's t or ANOVA tests when appropriate. $p < 0.05$ was considered as statistically significant. Statistical software consisted of SPSS version 19.0 (IBM Corporation).

RESULTS

The general characteristics of the participating women are depicted in Table 1. The cohort consisted of 101 women, with a mean age of 28.3 ± 4.9 years. 20 (20%) were evaluated in the first trimester of pregnancy (mean gestational age 11.2 ± 1 weeks), 47 (47%) in the second trimester of pregnancy (mean gestational age 18.1 ± 3.4 weeks), and 34 in the third trimester of pregnancy (mean gestational age 30.4 ± 4.1 weeks). There was a slight predominance of nulliparous (58.4%) women with white skin color (60.4%) in the cohort and the majority (90.1%) were non-smokers. Mean thyroid volume was 5.99 ± 1.78 mL for those evaluated in the first trimester, 6.36 ± 1.68 mL for those evaluated in the second trimester, and 6.06 ± 1.71 mL for those evaluated in the third trimester (p = 0.63). Thyroid hormone levels were

Table 1. General characteristics of pregnant women

Variable	
Maternal age, years (mean±SD)	28.3±4.9
Gestational age, weeks (mean±SD)	
– First trimester	11.2±1.0
– Second trimester	18.1±3.4
– Third trimester	30.4±4.1
Skin color, *n* (%)	
– White	61 (60.4)
– Black	12 (11.9)
– Mestizo	28 (27.7)
Parity, *n* (%)	
– Nulliparous	59 (58.4)
– Multiparous	42 (41.6)
Smoking habit, *n* (%)	
– Smokers	10 (9.9)
– Non-smokers	91 (90.1)
Thyroid volume, mL (mean±SD)	6.17±1.7
UIC, μg/L (median [IQR])	153.55 (85.58-221.42)
TSH, mIU/mL (mean±SD)	1.61±0.98
Total T4, nmol/L (mean±SD)	129±33.78
Total T3, nmol/L (mean±SD)	2.74±0.74
Free T4, pmol/L (median [IQR])	9.30 (5.6-41.7)
Free T3, pmol/L (median [IQR])	2.8 (0.7-18.5)
Thyroglobulin, ng/mL (median [IQR])	7.90 (0.3-228)
TPO-Ab, IU/L (median [IQR])	6.0 (6.0-1038)
Tg-Ab, IU/L (median [IQR])	30 (6.5-121.3)

TPO-Ab: thyroid peroxidase autoantibodies; Tg-Ab: thyroglobulin autoantibodies; IQR: interquartile range; UIC: urinary iodine concentration; SD: standard deviation.

Table 2. Iodine nutritional status in pregnant women

Iodine intake	n (%)	Urinary iodine excretion (μg/L) median (IQR)
Insufficient	44 (43.6)	115.6 (9.1-149)
Adequate	51 (50.5)	182.2 (150-243)
Above the requirements	6 (5.9)	263.7 (259.8-315.6)
Total	101 (100)	153.5 (85.58-221.42)

IQR: interquartile range.

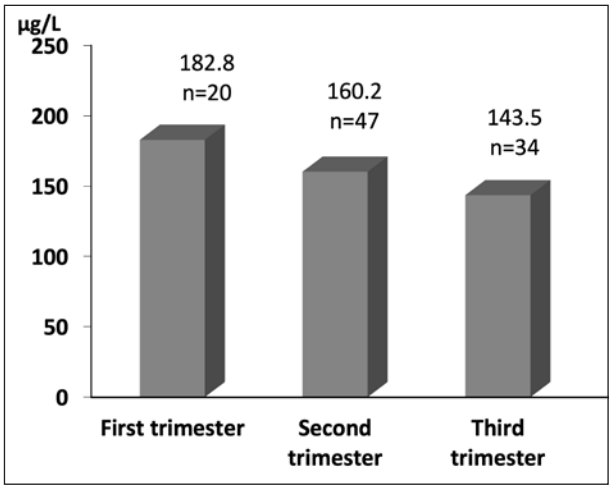

Figure 1. Urinary iodine concentrations according to the trimester of gestation. $p = 0.10$ (Kruskal–Wallis test).

normal in all women except for free T4 levels, which were slightly low (median 9.3 pmol/L [IQR 5.6-41.7]).

Iodine intake was categorized, based on urinary iodine excretion, as being below normal requirements in 43.6% of women (median 115.6 μg/L [IQR 9.1-149]), within normal requirements in 50.5% (median 182.2 [IQR 150-243]), and above normal requirements in 5.9% (median 263.7 [IQR 259.8-315.6]) (Table 2). The median urinary iodine excretion in the total cohort was 153.5 μg/L (IQR 85.58-221.42). Median urinary iodine excretion tended to be lower in women with more advanced pregnancies as shown in figure 1, although this did not reach statistical significance. A greater proportion of women in the third trimester of pregnancy were categorized as having an insufficient iodine intake (52.9% vs. 38% and 40% in the second and first trimester, respectively, $p = 0.02$) (Table 3).

Although median urinary iodine excretion decreased with advancing pregnancy, the differences did not reach statistical significance (Fig. 1 and Table 3). Urinary iodine excretion was similar between smokers and non-smokers and between Women with black and white skin color and did not correlate with maternal age ($r = 0.16$, $p = 0.87$), gestational age ($r = -0.18$, $p = 0.06$), number of pregnancies ($r = -0.12$, $p = 0.20$), or thyroid volume ($r = 0.15$; $p = 0.14$) (data not shown).

Table 4 depicts the results of thyroid function tests among women at the different stages of pregnancy. Mean TSH levels increased as gestational age progressed (first trimester 0.82 mIU/L, second trimester 1.71 mIU/L, and third trimester 1.92 mIU/L, $p = 0.00$) median free T4 levels were in the lower end of the normal range in women studied during the first trimester (10.75 pmol/L), whereas in those evaluated in the second and third trimesters, they were frankly below

Table 3. Categories of iodine nutritional status stratified by the trimester of pregnancy

Iodine intake	First trimester n (%)	Second trimester n (%)	Third trimester n (%)
Insufficient	8 (40)	18 (38.3)	18 (52.9)
Adequate	8 (40)	27 (57.4)	16 (47.1)
Above the requirements	4 (20)	2 (4.3)	0
Total	20 (100)	47 (100)	34 (100)

p=0.02 (χ^2 test).

Table 4. Thyroid function tests stratified by the trimester of pregnancy

Parameter	First trimester	Second trimester	Third trimester	p
TSH (mIU/L)*	0.82±0.47	1.71±0.99	1.92±0.95	0.00
Total T4 (nmol/L)*	134.16±52.5	130.55±24.6	123.9±31.04	0.52
Free T4 (pmol/L)†	10.75 (7.8-41.7)	9.35 (5.9-13.1)	8.35 (5.6-12.1)	0.00
Total T3 (nmol/L)*	2.83±1.37	2.67±0.47	2.78±0.51	0.73
Free T3 (pmol/L)†	2.65 (0.7-18.5)	3.05 (1.7-7.9)	2.85 (1.4-4.6)	0.54
Tg (ng/mL)	8.10 (2.1-228)	7.60 (1.2-36.1)	7.60 (1.3-27.3)	0.08

*Mean±SD; †median (interquartile range); Tg: thyroglobulin; SD: standard deviation; TSH: thyroid-stimulating hormone.

the normal range (9.35 and 8.35 pmol/L, respectively, p = 000). A similar trend was found for total T4, although this did not reach statistical significance (134.1, 130.5, and 123.9 nmol/L, respectively, p = 0.52). Tg levels also tended to be lower in women evaluated during the second and third trimesters than in those evaluated during the first trimester, without this reaching statistical significance. Neither total nor free T3 levels differed among women at the different stages of pregnancy. Free hypothyroxinemia was found in 71.1%, 66%, and 75% of women with insufficient, adequate, or above requirements iodine intakes, respectively (Table 5). Urinary iodine excretion correlated positively with free T4 (r = 0.28, p = 0.004) and free T3 (r = 0.31, p = 0.001), but no significant associations were found with TSH, total T4, or total T3 (data not shown).

Anti-TPO antibodies were present in 6.9% of the women, whereas 11.9% had anti-Tg antibodies and 4.9% had both. Subclinical hypothyroidism was found in 4.9% of the women in the cohort.

DISCUSSION

This study represents a preliminary report of a prospective research program that aims at including a total of 300 women, 100 in each trimester of pregnancy. Our findings suggest that despite an efficient salt iodization program, the urinary iodine excretion of over 40% of pregnant women barely reaches the lower limit of normal. This suggests that even though the ingestion of iodine-enriched salt may be sufficient to meet the requirements of the general population, this may not be the case for some pregnant women. Such relatively low iodine excretion in gestating women has been found before in cohorts from the United States[21], Brazil[22], Europe[6,17,23-25], as well as Asia[26-28] and Africa[29,30]. The National Health and Nutrition Survey[21] and a study from Brazil[22] report that 57% of pregnant women had evidence of a mildly insufficient iodine intake. The prevalence of such mildly insufficient iodine intake seems to have increased in the past years perhaps due to changes in the dietary habits of the population.

Interestingly, women with more advanced pregnancy tended to have a lower urinary iodine excretion although this did not reach statistical significance perhaps due to the relatively reduced number of studied subjects. This tendency is in concordance with an Iranian study that reported a progressive decline in the median urinary iodine excretion from 92.1 μg/L in the first trimester to 86.0 μg/L in the second trimester and finally to 76.8 μg/L in the third

Table 5. Thyroid function according to iodine intake in pregnant women, *n* (%)

Parameter	Iodine intake			p
	Insufficient *n*=38	Adequate *n*=47	Above the requirements *n*=4	
TSH				0.63
– Low	0	2 (4.3)	0	
– Normal	36 (94.7)	44 (93.6)	4 (100)	
– High	2 (5.3)	1 (2.1)	0	
Total T4				0.63
– Low	0	1 (2.1)	0	
– Normal	38 (100)	46 (97.9)	4 (100)	
Free T4				0.84
– Low	27 (71.1)	31 (66)	3 (75)	
– Normal	11 (28.9)	16 (34)	1 (25)	
Total T3				0.14
– Normal	32 (84.2)	45 (95.7)	4 (100)	
– High	6 (15.8)	2 (4.3)	0	
Free T3				0.82
– Low	5 (13.2)	5 (10.6)	0	
– Normal	33 (86.8)	41 (87.3)	4 (100)	
– High	0	1 (2.1)	0	
Thyroglobulin	*n*=37	*n*=42	*n*=5	0.82
– Low	1 (2.7)	2 (4.8)	0	
– Normal	28 (75.7)	32 (76.2)	3 (60)	
– High	8 (21.6)	8 (19)	2 (40)	

trimester[26]. Similarly, another study from Norway found that urinary iodine excretion dropped from 84 μg/L in the second trimester to 39 μg/L 3 days after delivery[31]. In contrast, a study from Mexico did not find significant differences in urinary iodine excretion among women in different stages of pregnancy[32]. Biologically, the apparently higher iodine requirement of women in the later stages of pregnancy may be the consequence of the continuous transfer of iodine and thyroid hormones from the mother to the fetus, even though the fetal thyroid is capable of producing its own hormone. As pregnancy progresses, the maternal iodine reserves are exhausted if there is not an adequate intake.

The progressive decline in free T4 levels and its correlation with a corresponding reduction in urinary iodine excretion has been reported before by other authors[28]. During the first trimester of pregnancy, the high concentrations of placental hCG stimulate the TSH receptor and lead to an increased thyroid hormone production. The resulting transient increment in free T4 levels is accompanied by a reciprocal fall in TSH[4]. As pregnancy progresses and the TBG levels rise, more thyroid hormone production is required to maintain free T4 levels. The increased activity of placental deiodinase, converting T4 into rT3 and T3 into T2, contributes further to the high thyroid hormone demand found in pregnancy[5]. However, in this study, a decrease in free T4 was observed, but not in total hormones. Thus, although the decline in free T4 levels makes physiological sense, it is possible that there is no correspondence between the reference intervals of the assay (European origin) and the values of the Cuban population, as there are no method-specific and trimester-specific reference ranges recommended in an optimal evaluation[12]. These ranges are also influenced by the iodine nutrition. An analytical error cannot be ruled out either since we measured this hormone by direct immunoassay

and not by the more reliable method of equilibrium dialysis. Pregnant women's serum has higher concentrations of TBG and non-esterified fatty acids and lower concentrations of albumin. Many free T4 immunoassays do not consider the effect of dilution[33].

Tg was not modified in any of the categories of iodine intake. Although a strong negative correlation of this protein with the urinary iodine concentration (UIC) has been demonstrated in the general population, the results obtained in pregnant women are contradictory[19,34,35]. It has been suggested that in areas with iodine deficiency, Tg increases its serum concentrations and in sufficient regions, it does not have significant changes, which means that it could be used in pregnancy as a marker of long-term iodine deficiency (weeks or months)[19,36].

We could not find any ultrasonographic evidence of thyroid enlargement. In fact, we found thyroid volumes that were slightly lower than those reported for non-pregnant Cuban women[37]. It must be pointed out, however, that the goitrogenic effect of pregnancy has been only reported in women living in iodine-deficient areas[7].

CONCLUSIONS

The population of pregnant women studied has adequate iodine nutrition, although close to the deficiency, which is evident in the third trimester. UIC is not related to the epidemiological variables studied or thyroid function or volume.

This study was a first approach to iodine nutrition in healthy pregnant women from Plaza Municipality. This allowed to recognize the situation of this topic and represents a starting point for future research. We consider that the main limitation of this study is its cross-sectional design, which did not allow evaluating the same woman at different moments of pregnancy. In addition, no reference ranges of thyroid function parameters were used for the Cuban population, so thyroid function was not optimally evaluated.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest in this study.

REFERENCES

1. World Health Organization. Guideline: fortification of Food-Grade Salt with Iodine for the Prevention and Control of Iodine Deficiency Disorders. Geneva: World Health Organization; 2014.
2. de Escobar GM, Obregon MJ, del Rey FE. Role of thyroid hormone during early brain development. Eur J Endocrinol. 2004;151 Suppl 3:U25-37.
3. Glinoer D. The importance of iodine nutrition during pregnancy. Public Health Nutr. 2007;10:1542-6.
4. Hershman JM. Physiological and pathological aspects of the effect of human chorionic gonadotropin on the thyroid. Best Pract Res Clin Endocrinol Metab. 2004;18:249-65.
5. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev. 1997;18:404-33.
6. Moreno-Reyes R, Glinoer D, Van Oyen H, Vandevijvere S. High prevalence of thyroid disorders in pregnant women in a mildly iodine-deficient country: a population-based study. J Clin Endocrinol Metab. 2013;98: 3694-701.
7. Rasmussen NG, Hornnes PJ, Hegedüs L. Ultrasonographically determined thyroid size in pregnancy and post partum: the goitrogenic effect of pregnancy. Am J Obstet Gynecol. 1989;160:1216-20.
8. Terry B. Consideraciones epidemiológicas de los desórdenes por deficiencia de yodo, criterios de evaluación y control. Rev Cubana Hig Epidemiol. 2008;46. Available from: http://www.scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1561-30032008003000010&lng=es&nrm=iso&tlng=es. [Last accessed on 2016 Apr 19].
9. Fernández SB, Martín EA. Estudio de la función tiroidea en embarazadas con bocio no tóxico. Rev Cub Obst Ginecol. 1985;11:36-43.
10. Ohashi T, Yamaki M, Pandav CS, Karmarkar MG, Irie M. Simple microplate method for determination of urinary iodine. Clin Chem. 2000;46:529-36.
11. Brunn J, Block U, Ruf G, et al. Volumetric analysis of thyroid lobes by real-time ultrasound (author's transl). Dtsch Med Wochenschr. 1981;106:1338-40.
12. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American thyroid association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21:1081-125.
13. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012;97:2543-65.
14. Dosiou C, Medici M. Maternal hypothyroxinemia during pregnancy. Eur J Endocrinol. 2017;176:21-38.
15. Pedersen KM, Börlum KG, Knudsen PR, et al. Urinary iodine excretion is low and serum thyroglobulin high in pregnant women in parts of Denmark. Acta Obstet Gynecol Scand. 1988;67:413-6.
16. Brucker-Davis F, Ferrari P, Gal J, et al. Iodine status has no impact on thyroid function in early healthy pregnancy. J Thyroid Res. 2012;2012: 168764.

17. Raverot V, Bournaud C, Sassolas G, et al. Pregnant French women living in the Lyon area are iodine deficient and have elevated serum thyroglobulin concentrations. Thyroid. 2012;22:522-8.
18. Brough L, Jin Y, Shukri NH, et al. Iodine intake and status during pregnancy and lactation before and after government initiatives to improve iodine status, in Palmerston north, New Zealand: a pilot study. Matern Child Nutr. 2015;11:646-55.
19. Ma ZF, Skeaff SA. Thyroglobulin as a biomarker of iodine deficiency: a review. Thyroid. 2014;24:1195-209.
20. WHO/UNICEF/ICCIDD. Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination: A Guide for Program Managers. 3rd ed. Geneva: World Health Organization; 2007.
21. Caldwell KL, Makhmudov A, Ely E, Jones RL, Wang RY. Iodine status of the U.S. Population, national health and nutrition examination survey, 2005-2006 and 2007-2008. Thyroid. 2011;21:419-27.
22. Ferreira SM, Navarro AM, Magalhães PK, Maciel LM. Iodine insufficiency in pregnant women from the state of São Paulo. Arq Bras Endocrinol Metabol. 2014;58:282-7.
23. Jiskra J, Fait T, Bílek R, et al. Mild iodine deficiency in women after spontaneous abortions living in an iodine-sufficient area of Czech republic: prevalence and impact on reproductive health. Clin Endocrinol (Oxf). 2014;80:452-8.
24. Zimmermann MB, Gizak M, Abbott K, Andersson M, Lazarus JH. Iodine deficiency in pregnant women in Europe. Lancet Diabetes Endocrinol. 2015;3:672-4.
25. Bath SC, Sleeth ML, McKenna M, et al. Iodine intake and status of UK women of childbearing age recruited at the university of Surrey in the winter. Br J Nutr. 2014;112:1715-23.
26. Delshad H, Touhidi M, Abdollahi Z, et al. Inadequate iodine nutrition of pregnant women in an area of iodine sufficiency. J Endocrinol Invest. 2016;39:755-62.
27. Fuse Y, Shishiba Y, Irie M. Gestational changes of thyroid function and urinary iodine in thyroid antibody-negative Japanese women. Endocr J. 2013;60:1095-106.
28. Yoganathan T, Hettiarachchi M, Arasaratnam V, Liyanage C. Maternal iodine status and the thyroid function of pregnant mothers and their neonates in Jaffna district of Sri Lanka. Indian J Endocrinol Metab. 2015;19:817-23.
29. Simpong DL, Adu P, Bashiru R, et al. Assessment of iodine status among pregnant women in a rural community in Ghana a cross sectional study. Arch Public Health. 2016;74:8.
30. Sadou H, Seyfoulaye A, Malam Alma M, Daouda H. Inadequate status of iodine nutrition among pregnant women residing in three districts of Niamey, the Niger republic's capital. Matern Child Nutr. 2014;10:650-6.
31. Berg V, Nøst TH, Skeie G, et al. Thyroid homeostasis in mother-child pairs in relation to maternal iodine status: the MISA study. Eur J Clin Nutr. 2017;71:1002-7.
32. García-Solís P, Solís-S JC, García-Gaytán AC, et al. Iodine nutrition status in pregnant women in Mexico. Thyroid. 2011;21:1367-71.
33. Toft AD, Beckett GJ. Measuring serum thyrotropin and thyroid hormone and assessing thyroid hormone transport. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's The Thyroid: A Fundamental and Clinical Text. 9th ed. Philadelphia, PA: Lippincott, Williams and Wilkins; 2005. p. 329-44.
34. Vejbjerg P, Knudsen N, Perrild H, et al. Thyroglobulin as a marker of iodine nutrition status in the general population. Eur J Endocrinol. 2009;161:475-81.
35. Koukkou E, Ilias I, Mamalis I, Adonakis GG, Markou KB. Serum thyroglobulin concentration is a weak marker of iodine status in a pregnant population with iodine deficiency. Eur Thyroid J. 2016;5: 120-4.
36. Bath SC, Pop VJ, Furmidge-Owen VL, Broeren MA, Rayman MP. Thyroglobulin as a functional biomarker of iodine status in a cohort study of pregnant women in the United Kingdom. Thyroid. 2017;27: 426-33.
37. Turcios S, Lence-Anta JJ, Santana JL, et al. Thyroid volume and its relation to anthropometric measures in a healthy Cuban population. Eur Thyroid J. 2015;4:55-61.