Serum Thyroglobulin Concentration Is a Weak Marker of Iodine Status in a Pregnant Population with Iodine Deficiency

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Key Words

Human chorionic gonadotropin · Iodine · Iodine deficiency · Pregnancy · Thyroglobulin

Abstract

Objective: To assess the reliability of thyroglobulin (Tg) as a marker of iodine status during pregnancy. **Design:** 299 women aged 30.5 ± 4.8 years (mean $\pm$ SD) were studied.

Methods: In every subject, we measured urinary iodine concentration (UIC), serum thyrotropin (TSH), Tg, free thyroxine (fT₄), Tg autoantibodies (TgAbs) and human chorionic gonadotropin (hCG) levels. We excluded samples with increased TgAbs from the analysis. **Results:** According to WHO criteria, the study population was iodine deficient in every trimester. Serum Tg levels did not differ during the three trimesters of pregnancy. Serum hCG levels fell significantly as pregnancies advanced. A weak, significantly negative correlation (limited to the 3rd trimester) was found between Tg and UIC ($p = -0.187$, $p = 0.039$). Serum fT₄ decreased as pregnancies advanced and TSH increased. Serum fT₄ was negatively correlated with TSH ($p = -0.161$, $p = 0.006$) and positively with hCG ($p = +0.165$, $p = 0.005$). The multiple regression equation of Tg based on hCG, TSH, UIC and trimester of pregnancy was significant but weak ($F = 4.057$, $p = 0.003$; $R^2 = 0.055$), with hCG as a significant predictor Tg

(p for log hCG = 0.041). **Conclusions:** Tg cannot be considered as a valid marker of iodine deficiency in pregnancy, at least in a mildly iodine-deficient environment. Further studies in a larger patient cohort with differences in iodine status, as well as studies on Tg changes after improving iodine status in pregnant women, are needed in order to corroborate these results.

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Introduction

Iodine is an essential mineral for thyroid hormone synthesis, but many populations worldwide continue to experience iodine deficiency. Deficiency in iodine occurs more often in women than in men, and is more common in pregnant women and older children [1, 2]. It is well documented that severe dietary maternal iodine deficiency in pregnancy is responsible for poor obstetric outcomes and neurodevelopment of the offspring [3–5], but it also appears that even mild-to-moderate iodine deficiency is associated with poorer intelligence quotient, reading scores [6] and spelling ability [7] in children up to the age of 9 years.

When normal absorption (approx. 90%) of dietary iodine is assumed, iodine status is traditionally, according

Table 1. Measured parameters by trimester of pregnancy [25th percentile/median/75th percentile (only subjects with negative anti-Tg)]

	Trimester		
	first (n = 85)	second (n = 74)	third (n = 123)
UIC, µg/l Range	88.6/124.3/190.4 30.1–628.1	92.2/133.7/187.6 8.9–540.4	88.2/125.5/177.6 18.6–431.5
Tg, ng/ml Range	10.8/14.9/23.4 0.6–81.9	9.2/16.7/22.3 0.6–62.5	10.7/18.5/28.9 0.5–185.1
hCG, mIU/ml × 10 ³ Range	16.3/34.2/69.1 0.9–219.0	6.3/11.2/23.6* 0.4–149.4	6.8/13.6/24.8* 0.6–69.9
* p < 0.05, first vs. second and third trimester (Kruskal-Wallis test).			

to the WHO recommendations, assessed using urinary iodine concentration (UIC) [8]. This can be measured either over 24 h or as a morning spot collection, and can be expressed either per gram creatinine or micrograms per liter. However, because UIC is highly influenced by recent iodine intake, it can only be used to determine iodine status for populations and not for individuals [9].

Serum thyroglobulin (Tg) may also be a suitable marker of the current iodine status in a population because it increases when iodine supply to the thyroid is low [10]. Tg levels in populations where endemic goiter is prevalent may be positively affected by thyroid cell mass and thyrotropin (TSH) [11]. However, at least two known parameters can affect serum Tg estimation. Firstly, serum Tg autoantibodies (TgAbs), which are increased in approximately 10% of the general population, can falsely alter serum Tg measurements. Secondly, during the first trimester of pregnancy, the levels of human chorionic gonadotropin (hCG) are highly increased and stimulate thyroid function and hormone production by binding to the TSH receptor [12]. It is well known that TSH receptor stimulation results in increased production of both thyroid hormones and Tg.

Therefore, the aim of our study was to assess the reliability of Tg as a marker of iodine status during pregnancy.

Subjects and Methods

Two hundred and ninety-nine women, who consecutively attended the antenatal clinics at the Elena Venizelou Maternity Hospital in Athens (approx. two thirds of the subjects) and the

Department of Obstetrics and Gynecology of the University of Patras from January 2014 to January 2015, were included in the study. Each subject gave her informed consent after full explanation of the purpose and nature of all procedures used and each woman was recorded once. Their mean age ± SD was 30.5 ± 4.8 years. Ninety-one women were examined in the first, 83 in the second and 125 in the third trimester of pregnancy. All subjects were living in the urban areas of Athens and Patras. In a recent prior study, these areas were found to be regions of mild nutritional iodine deficiency [13]. In every subject, we measured UIC in a morning (spot) urine sample with a colorimetric assay using the Sandell-Kolthoff reaction [14]. Serum TSH, Tg, free thyroxine (fT₄), TgAbs and hCG levels were also measured in the same morning blood sample using electro-chemiluminescence (Cobas E-411; Roche, Basel, Switzerland). Spot urine samples and blood samples were obtained during the morning clinic visit. All specimens were stored at –20°C until assayed. All the samples were analyzed in the Laboratory of the University of Patras.

To avoid possible interactions between Tg and anti-Tg, we excluded samples from 17 women with increased anti-Tg from the analysis. Normality in the value distribution of the measured variables was assessed with the Kolmogorov-Smirnov test; in all, with the exception of fT₄, normality of distribution was rejected. Differences by trimester in Tg, UIC, TSH and hCG were assessed using the Kruskal-Wallis test and analysis of variance (ANOVA) for fT₄. Tg as a function of UIC, TSH and hCG was evaluated with Spearman's rank correlation. Multiple linear regression was done to predict the participants' log-transformed Tg values based on log hCG, log TSH, log UIC and trimester of pregnancy (the last coded as 1 = first, 2 = second and 3 = third trimester, respectively). log transformations were done to normalize the distribution of continuous variables. Statistical significance was set at p < 0.05 for each statistic (with a Bonferroni correction where necessary).

The local ethics committees at the hospitals approved the study.

Fig. 1. Scatter plots of Tg versus UIC by trimester of pregnancy. **a** First trimester. **b** Second trimester. **c** Third trimester.

Table 2. Measured parameters by trimester of pregnancy [25th percentile/median/75th percentile for TSH and means $\pm$ SD for fT₄ (only subjects with negative anti-Tg)]

	Trimester		
	first (n = 85)	second (n = 74)	third (n = 123)
TSH, mIU/l	1.04/1.54/1.93	1.11/1.64/1.99	1.19/1.61/2.08
Range	0.01–3.41	0.04–5.47	0.29–5.05
fT ₄ , ng/dl	1.17 $\pm$ 0.17	0.96 $\pm$ 0.17*	0.90 $\pm$ 0.14*
Range	0.84–1.84	0.62–1.61	0.59–1.34

* $p < 0.05$, first vs. second and third trimester, second vs. third trimester (ANOVA).

Results

The measurement of UIC confirmed that the study population was UIC deficient in every trimester; serum Tg levels did not differ significantly during the three trimesters and serum hCG levels fell significantly as pregnancies advanced (table 1). A weak but statistically significant negative correlation was found between Tg and UIC in the whole sample ($\rho = -0.138$, $p = 0.020$), but when analyzing the data separately for each trimester, this weak negative association was limited to the third trimester ($\rho = -0.09$, $p = 0.39$; $\rho = -0.115$, $p = 0.32$, and $\rho = -0.187$, $p = 0.039$, for the first, second and third trimester, respectively) (fig. 1). Serum fT₄ decreased significantly as pregnancies advanced and TSH increased, respectively (table 2). Serum fT₄ was negatively correlated to TSH ($\rho = -0.161$, $p = 0.006$) and positively to hCG ($\rho = +0.165$, $p = 0.005$). The multiple regression equation, for log-transformed Tg values based on log hCG, log TSH, log UIC and trimester of pregnancy was significant, but weak ($F = 4.057$, $p = 0.003$; $R^2 = 0.055$, with $\log Tg = 0.989 + 0.093 \cdot \log hCG - 0.144 \cdot \log TSH - 0.157 \cdot \log UIC + 0.069 \cdot \text{trimester}$). Only hCG and trimester of pregnancy were significant predictors of Tg (p for $\log hCG = 0.041$, $\log TSH = 0.074$, $\log UIC = 0.084$ and for trimester of pregnancy = 0.016).

Discussion

In this study, using the WHO criteria for UIC [8], we confirmed our previous findings that pregnant women in Greece are iodine deficient in all trimesters [15, 16]. Us-

ing serum Tg as marker of iodine status in the same population, we found that Tg was negatively correlated with UIC only in the third trimester, and this correlation was weak. In nonpregnant populations, adults or children, it is well established that the above correlation is negative and strong [17, 18]. In pregnancy, studies on the Tg-UIC association are limited and they mainly focus on the establishment of a possible cutoff level for Tg as an indicator of iodine deficiency [19–26]. Most of these studies state that iodine-deficient pregnant women have a median Tg ≥ 13 $\mu\text{g/l}$.

Inadequate maternal iodine intake during pregnancy may be detrimental to the fetus [27], resulting in possible problems in psychomotor development [28, 29]. Since iodine deficiency is considered to be a worldwide problem [27, 30], an assessment of adequate iodine nutrition is needed, particularly in regions with known high rates of nutritional iodine deficiency. The commonly used UIC may be cumbersome for assessing iodine status in pregnancy [8], whereas serum Tg has been proposed to be an alternative, especially because it reflects long-term iodine status whereas UIC reflects iodine intake at a certain time point. This is due to the fact that in subjects with a iodine-deficient status TSH production is increased and triggers increased Tg release into the bloodstream [31, 32].

An issue that usually arises in the measurement of Tg is the increased level of anti-TgAbs, and, depending on the methodology used, can result in either higher or lower Tg values than the actual value [33, 34]. Therefore, in our study, we excluded samples with increased TgAbs levels from the analysis.

Another issue in the use of Tg as a marker of iodine status in pregnancy is the presence of hCG. The α subunit of hCG is almost identical to that of TSH [35], and therefore there is cross-reactivity between these hormones [35, 36]. Although the affinity of hCG for the TSH receptor is approximately 4,000 times less than that of TSH, this is enough to stimulate increased production and secretion of T_4 during the first trimester when hCG levels are high [35]. In our study, these physiological changes were also seen as serum fT_4 decreased significantly as pregnancies advanced, with a concomitant increase in TSH, and fT_4 was negatively correlated with TSH. hCG was high in the first trimester, decreased significantly over the second and the third trimester, as expected, and was a significant predictor for Tg. Serum Tg did not significantly change over the three trimesters and remained at levels slightly higher than 13 ng/l. Tg levels below this threshold are indicative of adequate daily iodine intake of 150 $\mu\text{g/l}$ [17, 18]. At the same time, Tg had a negative correlation, al-

though weak, with UIC only at the third trimester. It appears that serum Tg levels reflect the interaction of two stimulatory effects on thyrocytes in pregnancy: in the first trimester, the weak effect of the highly increased hCG levels and the strong effect of the decreased TSH levels and vice versa during the third trimester. That may explain the mild correlation we found – during the third trimester only – between Tg and its main secretory stimulus of iodine status, as expressed by UIC. Thus, despite the fact that median Tg levels during pregnancy were slightly above the suggested threshold of 13 ng/l of adequate iodine intake and that median UIC levels were slightly below the suggested WHO threshold (150 $\mu\text{g/l}$) of adequate iodine intake, the mild correlation between UIC and Tg we found, along with the broad distribution of the measurements, suggests that Tg is of limited value as a marker of iodine status in those individuals. Moreover, it is well established that iodine deficiency must be identified and treated at the beginning of pregnancy in order to avoid negative sequences on neurocognitive development of the fetus [37]. Finally, UIC was not significantly different in the three trimesters. This confirms our previous findings [13] and questions the tenet that renal iodine excretion increases during pregnancy [38].

In conclusion, our results indicate that, at least in an environment with mild iodine deficiency, Tg cannot be considered as a valid marker of iodine deficiency in pregnancy and thus cannot help in the prompt prevention of its sequences. Further studies including more subjects and environments with differences in the iodine status assessing the same women over the three trimesters, as well as studies on Tg changes after improving iodine status in pregnant women, are needed in order to corroborate these results.

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Disclosure Statement

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

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