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Pregnant Greek Women May Have a Higher Prevalence of Iodine Deficiency than the General Greek Population

Eftychia G. Koukkou[a] Ioannis Ilias[a] Irene Mamalis[b] Kostas B. Markou[b]

[a]Endocrine Unit, E Venizelou Hospital, Athens, and [b]Division of Endocrinology, University Medical School, University Hospital, Rion-Patras, Greece

Key Words
Pregnancy · Iodine · Greece

Abstract
Background: Adequate dietary iodine consumption, predicted via the urinary iodine concentration (UIC), is necessary for normal thyroid function and for the neurodevelopment of fetuses and neonates. The general population of Greece is considered to be iodine sufficient, but our preliminary findings suggest that Greek pregnant women are at risk of iodine deficiency. ***Objective:*** Our aim was to estimate the thyroid function and UIC in a representative population of pregnant Greek women. ***Methods:*** UIC and thyroid function were assessed in 1,118 women from 19 representative areas of the country. ***Results:*** The median UIC was found to be 127.1 μg/l (range 7.8–2,296), which is indicative of insufficient iodine intake according to the standard of the World Health Organization (WHO) for pregnant women. The median UIC was below the minimal recommended value of 150 μg/l in 61% of the women, and below 100 or 50 μg/l in 32 and 7%, respectively. An optimal iodine intake (150–250 μg/l) was observed in 26%, and was over the cut-off of 500 μg/l in 2% of the subjects. Serum thyrotropin significantly increased between trimesters, from 1.57 ± 1.2, to 1.68 ± 1.0 and to 2.02 ± 1.2 mU/l ($p < 0.001$). Serum-free thyroxine decreased significantly between trimesters, from 1.22 ± 0.34, to 1.01 ± 0.21 and 0.96 ± 0.2 ng/ml ($p < 0.05$). Serum thyroglobulin levels remained unchanged over the trimesters and were not correlated with UIC. ***Conclusions:*** While the general population of Greece is iodine sufficient, these findings suggest that, according to the WHO, the majority of pregnant Greek women are iodine deficient. These data strongly suggest that a proactive policy should be developed to lower iodine deficiency risk in this population of women.

Introduction

Adequate dietary iodine consumption, as determined by the urinary iodine concentration (UIC), is necessary for a normal thyroid function. During pregnancy, iodine requirements are increased [1] as a result of both the normal increase of maternal thyroid hormone production and the transfer of iodine to the fetus for embryonic thyroid hormone production from approximately the 17th week onwards. Insufficient iodine intake during this period has negative effects on maternal thyroid homeosta-

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E-Mail karger@karger.com
www.karger.com/etj

Kostas B. Markou
6 Thisseos Street
GR–26500 Ovria Patras (Greece)
E-Mail markoukonst@upatras.gr

Table 1. Proportion of the study population with low UIC according to the WHO classification

UIC, μg/l	n = 1,118	%
<50	79	7
<100	355	32[a]
<150	680	61[a]
150–250	286	26
>250–500	125	12
>500	27	2

[a] Cumulative totals and percentages.

Table 2. No significant differences in UIC between trimesters

Trimester	1st (n = 292)			2nd (n = 241)			3rd (n = 585)		
Quartiles	Q1	Q2	Q3	Q1	Q2	Q3	Q1	Q2	Q3
UIC, μg/l	82	127	198	88	126	187	86	122	189

Table 3. TFTs over the pregnancy trimesters of the study population

	1st trimester (n = 255)	2nd trimester (n = 165)	3rd trimester (n = 432)	p
TSH, mU/l	1.57±1.2	1.68±1.0	2.02±1.2	<0.001
fT_4, pmol/l[a]	15.70±4.38	13.00±2.70	12.36±2.57	<0.05
Tg, ng/ml	16.5±14.1	15.4±11.3	18.4±18.9	n.s.

[a] pmol/l = ng/dl × 0.077688.

sis, as expressed by an increased thyrotropin (TSH) production and thyroid gland volume, which may result in the development of goiter [2]. Thyroglobulin (Tg), a glycoprotein comprising two 330-kDa protein chains synthesized in the thyrocyte, has a key role in the synthesis of thyroid hormones, and its synthesis and proteolysis are also increased under the influence of TSH in conditions of inadequate iodine supply.

Moreover, inadequate iodine intake during pregnancy has a negative effect on embryonic development and the psychosocial advancement of the infant. Non-placebo-controlled studies have found that this is particularly true when the iodine deficiency is severe, but also occurs in the presence of mild to moderate iodine deficiency [3–7] (placebo-controlled studies are currently ongoing). For the past 15 years Greece has been considered an iodine-sufficient country in terms of the general population [8]. Our preliminary findings suggest, however, that this may not be the case [9, 10]. In the present study we aimed to clarify this issue through larger-scale assessments of pregnant Greek women using UIC and thyroid function tests (TFTs).

Methods

The study protocol was approved by the Ethical committees of the Elena Venizelou Maternity Hospital in Athens, and the University Hospital of Patras, Greece. Our study population included a representative sample of 1,118 women (25th percentile, 28 years old; median, 31 years old; 75th percentile, 34 years old), regardless of the trimester of pregnancy, from 19 regions in Greece that included subjects from urban, suburban, rural, mainland, and island settings. Women taking iodine via supplementation (including multivitamins) were excluded from the study. Following the provision of written consent, each subject was assessed once during a regular morning visit at the obstetric clinic. Subject age and gestational age, based on the date of the last menstrual period, were registered. Blood and urine samples were collected at this visit and stored at –4°C until analysis. All analyses of the collected samples were performed at the same time. UIC was measured with a colorimetric assay using the Sandell-Kolthoff reaction [11] and TFTs were done with electrochemiluminescence (Cobas E-411; Roche, Basel, Switzerland) [11]. The intra- and interrun coefficient of variation for the Tg measurements were 2.0–4.8 and 4.0–5.9%, respectively. Statistical analyses included analysis of variance, analysis of covariance, Spearman's ρ and the Kruskal-Wallis test.

Results

The median UIC was 127.1 μg/l (range 7.8–2,296), which is indicative of iodine deficiency according the World Health Organization (WHO) criteria for pregnant women [11]. A median UIC of <150 μg/l was found in 61% of the women, and a UIC below 100 and 50 μg/l were found in 32 and 7% of the study population, respectively (table 1). An optimal iodine status (150–250 μg/l) was observed in 26%, and levels over the cut-off of 500 μg/l were detected in 2% of the subjects. No differences were found in UIC among the trimesters of pregnancy (table 2). The highest UIC levels (median, range) were measured in one area in Thessaly (172 μg/l, 42–584), one area in eastern Macedonia (175 μg/l, 44–805) and in one area in Thrace (155 μg/l, 91–393); the lowest were observed in Central Macedonia (93 μg/l, 15–281) and in Zakynthos, an Ionian Sea island (96 μg/l, 9–551; fig. 1).

Fig. 1. Geographical distribution of the examined areas.

Serum TSH increased over the pregnancy trimesters from 1.57 ± 1.2 (first) to 1.68 ± 1.0 (second) and 2.02 ± 1.2 mU/l (third; $p < 0.001$), and serum-free thyroxine (fT_4) decreased from 1.22 ± 0.34 (first) to 1.01 ± 0.21 (second) and 0.96 ± 0.2 ng/ml (third; $p < 0.05$). Serum Tg levels did not change significantly during the trimesters (16.5 ± 14.1, 15.4 ± 11.3 and 18.4 ± 18.9 ng/ml, respectively) and were not significantly correlated with UIC (table 3).

Discussion

Our study clearly demonstrates that, in a representative sample of pregnant Greek women, the daily intake of iodine in a significant proportion (nearly 66%) is <150 μg/l, which is the cut-off level set by the WHO as the minimal acceptable value in pregnancy [11]. Furthermore, ~33% of the studied population had a daily iodine status below 100 μg/l, while only a quarter of the examined women were iodine sufficient according to the WHO criteria for pregnancy. There was no geographical distinction between the low and adequate iodine status regions. Low iodine intake was observed in both urban and rural areas on the mainland and the islands. However, it is notable that of the 19 examined areas, only 1 of the 3 with an optimal iodine status was located by the coast. Perhaps this reflects the relatively low seaweed abundance around Greek shores [12]. These findings put into question the historical understanding that populations living in mountainous regions are more at risk of poor iodine status than populations living near the sea. [11].

Iodine plays a vital role during pregnancy as thyroid hormones are essential for the normal development of the fetal central nervous system. Although the fetal thyroid gland begins to produce thyroxine by the 12th week of pregnancy, this production, even during the 2nd and 3rd trimesters, may only be partially sufficient to satisfy fetal requirements. The continuous supply of iodine from the mother to the fetus via the placenta for the synthesis of fetal thyroid hormone strongly suggests that maternal iodine deficiency can be deleterious [3–5]. Therefore, an

optimal maternal thyroid function status is of great importance to help ensure normal fetal development [3–5].

Over recent decades the elimination of iodine deficiency in many countries has been achieved through significant proactive programs, but it is now clear that there is still work to be done. While it appears that iodine deficiency in the general population is no longer a concern, pregnant women seem to be at a relatively high risk of deficiency. This is likely due to the fact that iodine requirements during pregnancy are increased at a time in which iodized salt consumption is decreased [3–5]. Although the general Greek population is now considered to be iodine replete [4], the majority of the pregnant women included in this study were observed to have iodine deficiency according to the WHO criteria, and a significant proportion of them also had UIC levels below 100 μg/l. It should be pointed out that, as suggested by Zimmerman and Andersson [13], the use of these crude cutoffs may overestimate the prevalence of iodine deficiency.

Our study TFTs identified expected changes, with serum TSH increasing as the stage of pregnancy advanced, and serum fT4 lowering correspondingly. On the contrary, serum Tg did not change during subsequent trimesters and was not correlated with UIC. Tg can be an easy-to-use marker of the current iodine status in a population, as its measurement is more straightforward than UIC estimation. However, in contrast to its use with the general population, serum Tg concentration in pregnancy is a weak and unreliable indicator of iodine status, at least in a mildly iodine-deficient population [10, 14]. This could be attributed to the known human chorionic gonadotropin interference and thyroid function stimulation during pregnancy [15, 16].

These results strongly imply that caregivers should take the responsibility of informing both pregnant women and women of childbearing age about the necessity of assuring an adequate iodine status, either through the consumption of high-iodine foods or through iodine supplementation, during this special period of their lives. The benefits of achieving and maintaining an adequate iodine status during pregnancy for the offspring are clear when reviewing documented cases with severe iodine deficiency [15, 16]. The question remains as to whether the implementation of such a policy will achieve similar beneficial outcomes without side effects in populations with mild iodopenia, and whether such a policy will be cost effective.

Liesenkötter et al. [17] administered 300 μg of potassium iodide per day in 38 pregnant women from 10–12 weeks onwards and found that this supplementation resulted in a smaller size of the neonatal thyroid gland and was not accompanied by increased autoimmunity, as expressed by the frequency of antithyroid peroxidase autoantibodies [15, 16]. Moreover, iodine replacement appears to reduce the maternal thyroid volume and, importantly, may improve the neurodevelopment and neurointellectual outcome of the offspring [15, 16]. It is understood that more randomized controlled trials of iodine supplementation in pregnancy are required in mild iodine-deficient areas. Meanwhile, the WHO and the Iodine Global Network (IGN) advise iodine supplementation during pregnancy and lactation [15, 16].

In conclusion, in the present study we found substantial iodine deficiency in pregnant women throughout Greece. Treatment of this deficiency is imperative and should proceed in a proactive fashion.

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Disclosure Statement

The authors have no conflicts of interest with respect to this study to disclose.

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