

Parameters of Thyroid Function Throughout and After Pregnancy in an Iodine-Deficient Population

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Background: The thyroid hormone milieu is of crucial importance for the developing fetus. Pregnancy induces physiological changes in thyroid homeostasis that are influenced by the iodine status. However, longitudinal studies addressing thyroid function during pregnancy and after delivery are still lacking in mild-to-moderate iodine-deficient populations. Here we characterize the serum parameters of thyroid function throughout pregnancy, and until 1 year after delivery, in a population of pregnant women whom we have previously reported to be iodine deficient (median urinary iodine levels below 75 $\mu\text{g/L}$).

Methods: One hundred eighteen pregnant women were studied. Clinical data were recorded and serum was collected. Serum total and free thyroxine (T_4) and triiodothyronine (T_3), thyroid-stimulating hormone, thyroxine-binding globulin, and thyroglobulin were measured.

Results: Mean total T_4 ranged from 159 at the start of gestation to 127 nmol/L at 1 year after delivery, free T_4 from 14.2 to 17.8 pmol/L, total T_3 from 2.4 to 2.1 nmol/L, free T_3 from 6.7 pmol/L to 6.4 pmol/L, thyroid-stimulating hormone from 1.2 to 1.4 mIU/L, T_4 -binding globulin from 62.0 to 26.9 mg/L, and thyroglobulin from 11 to 10 $\mu\text{g/L}$.

Conclusion: The pregnant women in this study had an absence of the usual free T_4 spike and a smaller than expected increment in total T_4 , described during pregnancy in iodine-sufficient populations. A greater number of women had subclinical hypothyroidism compared with iodine-sufficient populations. This hormonal profile, most likely due to iodine insufficiency, may result in inadequate thyroid hormone supply to the developing fetus. We conclude that care should be taken when reviewing the results of thyroid hormone tests in iodine-insufficient populations and when no gestation-specific reference values have been established. In addition, we recommend iodine supplementation in our population and populations with similar iodine status, particularly during pregnancy and lactation.

Introduction

PREGNANCY IS ASSOCIATED with profound modifications in the regulation of thyroid function and economy. These changes are the result of various factors: increase of thyroxine-binding globulin (TGB) due to elevated estrogen, elevated levels of human chorionic gonadotropin that has thyroid-stimulating hormone (TSH)-like activity, increased renal losses of iodine due to increased glomerular filtration rate, modifications in the peripheral metabolism of maternal thy-

roid hormones, and iodine transfer to the placenta (1,2). The physiologic adaptations that will optimize the maternal status for fetal development require adequate iodine intake. Iodine is essential for the synthesis of the thyroid hormones needed for the proper development of the central nervous system (1,2). Therefore, interpretation of thyroid tests during pregnancy should consider these physiologic changes and the iodine status of the population (2–4).

The fetus relies completely on maternal thyroid hormones until the onset of its own thyroid function at the end of the first

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trimester; the mother continues to supply thyroid hormones and iodine until birth, and iodine during lactation (1,2,5). Although severe iodine deficiency has long been known to cause mental retardation, increasing evidence shows that maternal hypothyroidism and maternal euthyroid hypothyroxinemia are related to poorer psychomotor development of the newborn (5–8). Therefore, recommendations on iodine supplementation prior and throughout pregnancy and until the end of lactation have been made by investigators and clinicians (9). This is particularly relevant, considering that many developed and developing countries are still considered iodine insufficient (9,10). Controversy exists, however, on whether to monitor thyroid function throughout pregnancy (11,12). A joint statement from the American Association of Clinical Endocrinologists, American Thyroid Association, and the Endocrine Society defends “routine screening for subclinical thyroid dysfunction in adults, including pregnant women and those contemplating pregnancy” (13). The Endocrine Society in their comments on management of thyroid dysfunction during pregnancy and postpartum states that “universal screening of pregnant women for thyroid disease is not yet supported by adequate studies. . .” (14,15). Finally, the American College of Obstetricians and Gynaecologists and the United States Preventive Services Task Force suggests “performing testing only in women with personal history or symptoms of thyroid disease and do not recommend universal testing” (16). A number of recent studies have been concerned with the cost-effectiveness of universal screening in pregnancy and the debate between “target high-risk case finding” and “universal screening” (17,18). Many agree that for proper monitoring it is necessary to establish reference ranges for pregnancy and to choose the most informative thyroid hormone parameters (3,4,12).

In the present study we characterized parameters of thyroid hormone function throughout pregnancy and after delivery in the same population of pregnant women we previously found to be mild-to-moderately iodine insufficient (19), as defined by the World Health Organization (WHO) criteria (20).

Materials and Methods

Subjects

The study was carried out at the hospital Centro Hospitalar do Alto Ave, EPE, Guimarães, Portugal, between January 2003 and December 2005. Guimarães is located 50 km from the sea, with both urban and rural populations, in a total of about 1.2 million inhabitants. One hundred forty consecutive pregnant women (without exclusion criteria, see below) entering the antenatal clinic were invited to perform thyroid function tests during and after pregnancy. Upon agreement, demographic and clinical details were collected, including age, gestational age, number of previous pregnancies, breastfeeding 3 months after delivery, and Graffar socioeconomic cultural state. A food-frequency questionnaire was used to ascertain the number of weekly fish meals (a relevant source of dietary iodine), the use of iodized salt or iodine-containing multivitamin pills, and whether the eating regimen was vegetarian. Exclusion criteria were the use of drugs or iodinated antiseptics, previous diabetes, assisted medical reproduction, malformations of the fetus, autoimmune disorders, thyroidal and other endocrine dysfunctions, and

heavy smoking (more than 10 cigarettes per day). Women with multiple pregnancies or with antithyroidal antibodies (antithyroglobulin [anti-Tg] and/or antiperoxidase [anti-TPO]) were later excluded from the analysis. A total of 118 pregnant women thus remained in the study.

All women enrolled gave informed written consent and the study was approved by the research ethical committee of the Centro Hospitalar do Alto Ave. We have previously characterized this population for iodine by measuring urine and breast milk iodine levels (19).

Thyroid function measures

Blood was collected in each trimester of pregnancy (12 ± 1 , 24 ± 1 , and 32 ± 1 weeks), when admitted to the hospital in labor, and at 3 days, 3 months, and 1 year after delivery. Blood was centrifuged and serum was kept at -80°C until use. The following serum parameters were measured: total thyroxine (TT_4), free T_4 (FT_4), total triiodothyronine (TT_3), free T_3 (FT_3), TSH, Tg, and anti-TPO and anti-Tg antibodies using the DYNOTest radioimmunoassay reagents from Brahms Diagnostica GmbH (Berlin, Germany): DYNOTest FT_4 (SPART), DYNOTest T_4 , DYNOTest T_3 , DYNOTest TSH, DYNOTest TgS, DYNOTest anti-TPO, and DYNOTest anti-Tgn. Manufacturer's normal reference ranges were TT_4 58–154 nmol/L, FT_4 10–25 pmol/L, TT_3 1.23–3.08 nmol/L, FT_3 3.4–8.5 pmol/L, TSH 0.3–4.0 mIU/L, Tg $<70 \mu\text{g/L}$, anti-TPO $<60 \text{U/mL}$, and anti-Tg $<60 \text{U/mL}$. For TBG the manufacturer provided a reference range for pregnancy of 16.4–64.4 mg/L. Conversion units used were as follows: FT_3 in pmol/L = (pg/mL)/0.651; FT_4 in pmol/L = (pg/mL)/0.777.

Subclinical hypothyroidism was defined as a serum TSH concentration above the statistically defined upper limit of the reference range (percentile [P] 97.5) when serum FT_4 concentration was within reference range, and overt hypothyroidism as serum TSH values $>P97.5$ and $\text{FT}_4 <P2.5$. Subclinical hyperthyroidism was defined as a serum TSH concentration below the statistically defined lower limit of the reference range (P2.5) when serum FT_4 concentration was within reference range, and overt hyperthyroidism as TSH values $<P2.5$ and $\text{FT}_4 >P97.5$. Isolated hypothyroxinemia when TT_4 or FT_4 values $<P2.5$ and TSH was normal (8).

Statistical analyses

Considering that some variables exhibited a much skewed distribution (Tg and TSH), the median was used as the measure of central tendency together with the interquartile range and percentiles. Correlations between variables were done using the Pearson's correlation or Spearman's rank correlation tests.

The comparison of several analytes throughout trimesters was conducted using repeated measures. In some cases (TT_3 , TSH, Tg), the log transformation was used so that the distributions were approximately normal. The assumption of sphericity was evaluated through the Mauchly's test, and when the test was significant, the degrees of freedom were corrected using the Greenhouse-Geisser estimate of sphericity. Pairwise comparisons were corrected with the Bonferroni method.

Statistical analyses were performed using the SPSS 15 software package (SPSS, Chicago, IL). Values were considered significant when $p < 0.05$. All tests were two sided.

Results

Demographic data

From the initial pool of 140 pregnant women, 15 were excluded for being positive for either anti-TPO or anti-Tg, 1 of these had a pregnancy loss, and 7 for multiple pregnancies (all twins). The remaining 118 women had a medium age of 29.9 years (standard deviation: 7.0) and were pregnant for an average of 2.3 times (standard deviation: 1.4), 55.9% belonged to a medium-high socioeconomical status, and 51.4% ate fish less than three times a week.

There was no difference between the thyroid function of women with anti-TPO and anti-Tg antibodies (10.7% of the study population) when compared with those without antibodies (data not shown).

Thyroid function throughout pregnancy and after delivery

Figure 1 represents the P10, P50, and P90 for all parameters measured in pregnant women in the first, second, and third trimesters, in the beginning of labor, and at 3 days, 3 months, and 1 year after delivery. It is expected that the values at 1 year after delivery represent the basal levels, because the effects of pregnancy should have disappeared (2,11,21). Because of the absence of FT₄ surge and of the small increment of TT₄, percentiles of these hormones were skewed to lower ranges. The detailed numerical values (median and interquartile range) of the thyroid function are presented in Table 1.

FT₄ levels during pregnancy were always lower than after delivery, whereas TT₄, TT₃, and TBG levels were higher during pregnancy than after delivery, although TT₄ increased only 25% above the basal level compared with the expected 50% (1–3,21). The molar ratio TT₃/TT₄ remained steady (0.016–0.017) throughout pregnancy.

Statistical analysis revealed significant differences across trimesters, albeit the small changes in median values. TT₄ values changed significantly between the first and the third trimesters, and the second and the third trimesters, whereas FT₄, FT₃, and TSH values changed significantly between all three trimesters (first and second, second and third, and first and third). TBG values changed significantly between the first and the second trimesters and between the first and the third trimesters, and Tg changed between the first and the third and between the second and the third trimesters.

Thyroidal dysfunction

In the first trimester of pregnancy two women had overt hyperthyroidism and one had overt hypothyroidism. The incidence of subclinical hypothyroidism changed according to different thresholds: if defined by TSH >P97.5 (3.99 mIU/L in this population) it was 1.7%, but if the value of 2.5 mIU/L was considered it was 7.6%. The same occurred with subclinical hyperthyroidism: 1.7% of the women had TSH values <P2.5 (0.08 mIU/L in this population) and 7.6% presented levels below the reference range provided by the manufacturer. It should be noted that during the first trimester of pregnancy, TSH levels are expected to decrease; therefore, a cutoff of 2.5 mIU/L may be still too high (3,4). In that case, the percentage of pregnant women displaying signs of subclinical hypothyroidism may be higher in our population.

Isolated hypothyroxinemia defined as TT₄ levels <P2.5 (97.0 nmol/L) was found in 1.7% of the pregnant women, but when the absolute value of TT₄ <100 nmol/L suggested in the literature was used, this number increased to 2.6%. There is no universal absolute value of FT₄ to define hypothyroxinemia (its value is dependent on the method and on the trimester of gestation) (3,4). It should be emphasized that these absolute reference values are for the nonpregnant population and that in the first trimester TT₄ and FT₄ are expected to increase while TSH is expected to decrease.

Table 2 shows the correlations between the various analytes studied. Of interest, the second trimester revealed fewer correlations than any other time point (TT₄ tended to correlate with FT₄, TT₃, and FT₃; TT₃ correlated with FT₃), and in the first trimester and 1 year after delivery there was a negative correlation between TT₃ and FT₄.

We also assessed correlations between thyroid function and demographic characteristics, and no major correlations were found (data not shown).

Discussion

To respond properly to the pregnancy's increased T₄ demand, several adaptations are triggered during pregnancy (1,2,5). These should not pose a major problem to the thyroid status of the pregnant women, and consequently to the fetal development, in iodine-sufficient populations. The present study focused on pregnant women (singleton and negative for antithyroid antibodies) from a mild-to-moderate iodine-insufficient area (19), as defined by the criteria established by the WHO (20): median urinary iodine in the three trimesters of pregnancy and milk iodine concentrations of <75 µg/L and <100 µg/L, respectively (19). Of note, this had an impact on the progeny of these women, because median neonatal urinary iodine was low (71 and 97 µg/L at 3 days and 3 months of age) (19). Here we have further extended the study to characterize serum parameters of thyroid function throughout pregnancy and up to 1 year after delivery, selecting from the initial pregnant population those singleton and negative for anti-TPO and anti-Tg antibodies. TT₄, TT₃, and TBG levels were higher during pregnancy than after delivery. However, the increase of TT₄ in the first trimester was small (25%), when compared with that expected (50%) in iodine-sufficient populations (1–3,21), and further decreased throughout pregnancy rather than remaining steady (21). The FT₄ levels did not show the termed "FT₄ first trimester surge" (1–3,21), instead these were always lower than basal levels throughout pregnancy and lower than other reports in iodine-sufficient populations (8,9). Of note, the peak of TSH before labor preceded that of Tg at 3 days after delivery, being exaggerated in those women with some thyroid insufficiency (those with TSH values in P90). In addition, if an absolute cutoff of 2.5 mIU/L TSH is considered, 8% of women in the first trimester of pregnancy are subclinically hypothyroid (3,22–25). As TSH levels normally decreased in the first trimester of pregnancy, the TSH cutoff of 2.5 mIU/L defined for nonpregnant women may still be too high for pregnant women (3,4) and, therefore, even more women in our pregnant population may display subclinical hypothyroidism. These observations are in accordance with the iodine insufficiency previously described in this population (19).

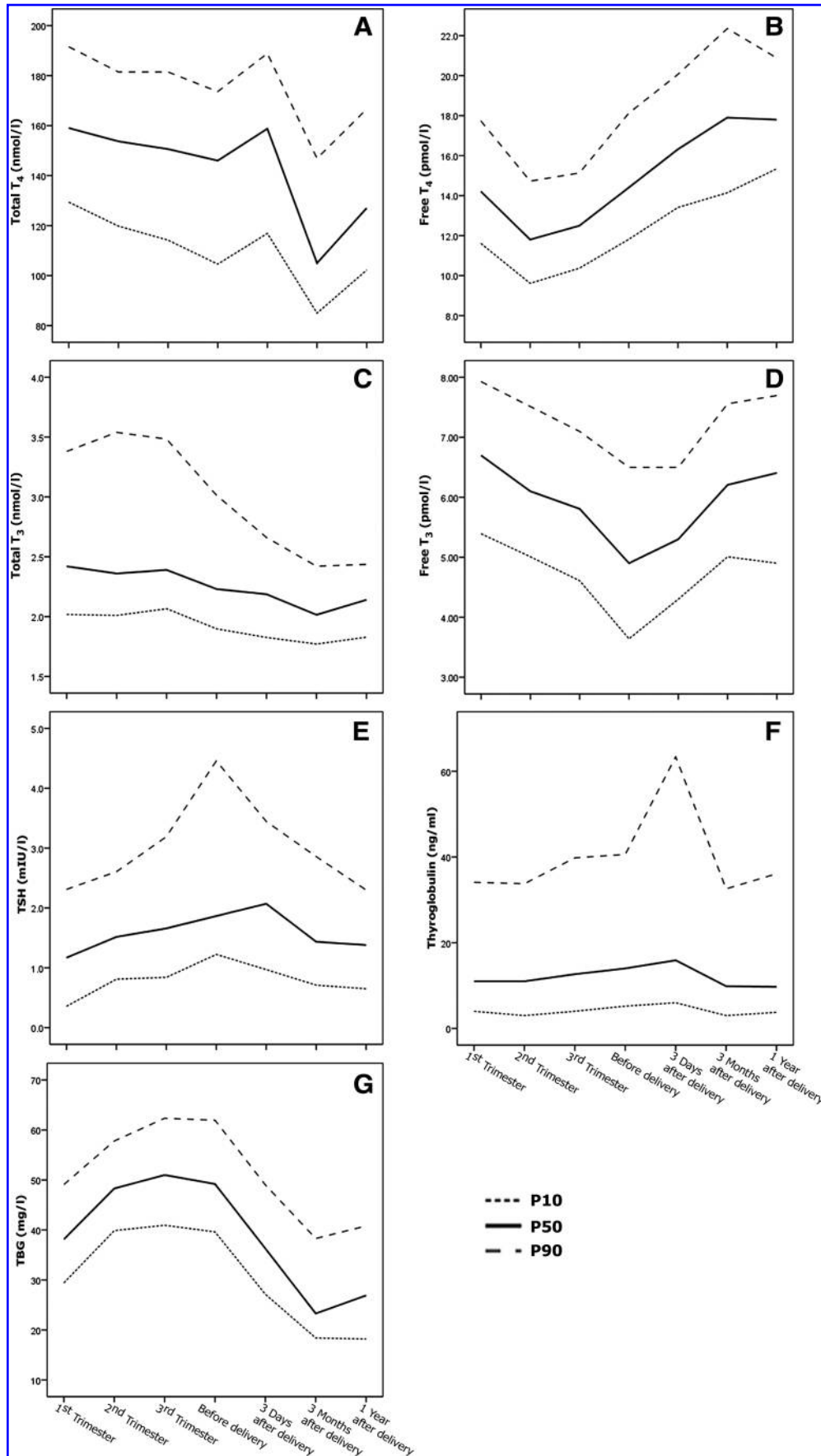


FIG. 1. Percentiles 10, 50, and 90 (P10, P50, P90) of thyroid analytes throughout and after pregnancy: TT₄ (A), FT₄ (B), TT₃ (C), FT₃ (D), TSH (E), thyroglobulin (F), TBG (G) in the first, second, and third trimesters, in the beginning of labor, and at 3 days, 3 months, and 1 year after delivery. TT₄, total thyroxine; FT₄, free T₄; TT₃, total triiodothyronine; FT₃, free T₃; TSH, thyroid-stimulating hormone; TBG, thyroxine-binding globulin.

TABLE 1. MEASUREMENTS OF THYROID FUNCTION THROUGHOUT PREGNANCY AND AT 1 YEAR AFTER DELIVERY (MEDIAN, P25, AND P75)

Analyte	First trimester	Second trimester	Third trimester	1 year after
TT ₄ (nmol/L)	(n = 117)	(n = 107)	(n = 105)	(n = 61)
Median	159.03	153.71	150.61	127.00
P25-75	144.36-172.56	137.00-167.86	128.12-166.15	110.50-147.50
FT ₄ (pmol/L)	(n = 117)	(n = 107)	(n = 105)	(n = 61)
Median	14.21	11.80	12.50	17.80
P25-75	12.78-16.10	10.46-13.66	11.48-13.71	16.31-19.31
TT ₃ (nmol/L)	(n = 118)	(n = 109)	(n = 105)	(n = 63)
Median	2.42	2.36	2.39	2.14
P25-75	2.20-2.86	2.19-2.84	2.25-2.75	2.00-2.30
FT ₃ (pmol/L)	(n = 116)	(n = 96)	(n = 98)	(n = 59)
Median	6.70	6.10	5.81	6.41
P25-75	6.02-7.22	5.50-6.79	5.21-6.41	5.50-7.10
TSH (mIU/L)	(n = 118)	(n = 104)	(n = 102)	(n = 59)
Median	1.17	1.52	1.66	1.38
P25-75	0.70-1.77	1.17-2.08	1.24-2.24	0.94-1.75
Tg (ng/mL)	(n = 117)	(n = 105)	(n = 105)	(n = 61)
Median	11.00	11.00	12.65	9.70
P25-75	6.84-19.20	5.50-16	7.00-21.94	5.95-20.35
TBG (mg/L)	(n = 112)	(n = 105)	(n = 104)	(n = 59)
Median	38.15	48.30	51.00	26.90
P25-75	33.13-43.45	44.45-53.75	45.43-56.68	20.90-35.80

TT₄, total thyroxine; FT₄, free T₄; TT₃, total triiodothyronine; FT₃, free T₃; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; TBG, thyroxine-binding globulin; P, percentile.

TABLE 2. CORRELATION COEFFICIENTS (SPEARMAN'S ρ) FOR THYROID ANALYTES IN PREGNANT WOMEN

	TT ₄	FT ₄	TT ₃	FT ₃	TSH	TBG	Tg
First trimester							
TT ₄	1						
FT ₄	0.34 ^a	1					
TT ₃	0.31 ^a	-0.29 ^a	1				
FT ₃	0.23 ^b	-0.10	0.43 ^a	1			
TSH	-0.30 ^a	-0.23 ^b	-0.08	-0.02	1		
TBG	0.29 ^a	-0.02	0.04	0.26 ^a	0.00	1	
Tg	0.07	-0.02	0.05	-0.10	-0.09	0.01	1
Second trimester							
TT ₄	1						
FT ₄	0.05	1					
TT ₃	0.34 ^a	0.03	1				
FT ₃	0.19	-0.13	0.19	1			
TSH	-0.09	-0.14	-0.06	0.00	1		
TBG	0.36 ^a	-0.16	0.13	0.40 ^a	0.09	1	
Tg	0.06	0.07	0.04	0.07	-0.07	-0.02	1
Third trimester							
TT ₄	1						
FT ₄	0.27 ^a	1					
TT ₃	0.56 ^a	-0.20 ^b	1				
FT ₃	0.44 ^a	0.00	0.61 ^a	1			
TSH	-0.22 ^b	-0.07	-0.22 ^b	-0.03	1		
TBG	0.52 ^a	-0.06	0.49 ^a	0.52 ^a	-0.05	1	
Tg	0.13	-0.02	-0.07	-0.05	-0.02	0.05	1
1 year after delivery							
TT ₄	1						
FT ₄	-0.15	1					
TT ₃	0.66 ^a	-0.47 ^a	1				
FT ₃	0.62 ^a	-0.21	0.70 ^a	1			
TSH	0.04	-0.16	0.09	-0.04	1		
TBG	0.79 ^a	-0.47 ^a	0.75 ^a	0.56 ^a	0.17	1	
Tg	0.17	0.02	0.13	0.22	0.06	0.07	1

^aCorrelation is significant at the 0.01 level.

^bCorrelation is significant at the 0.05 level.

We chose to recruit women from a public hospital for this study because most women in Portugal attend the public health system. However, caution should be taken when extrapolating these results to the general population given the small size of the studied population, the recruitment of women from a single hospital and region of Portugal, and the fact that these women are iodine deficient.

We and other investigators have determined the parameters of thyroid function at various moments throughout pregnancy, both in populations considered iodine sufficient (26,27) and insufficient (1,2,14,28). Nevertheless, to the best of our knowledge, the present study is the first considering as basal levels of thyroid function those at 1 year after delivery, for the same women. In addition, it is correspondingly the most extensive analysis for women for whom information on urinary and milk iodine levels and thyroid gland volumes is available.

Iodine deficiency remains a problem worldwide (20). In fact, none of the women in our study reported consumption of iodinated salt. This problem is twofold: (i) several countries, including Portugal and other coastal countries, do not follow the WHO recommendation on the use of household iodized salt or iodine supplementation (10,29) and, therefore, (ii) women are not knowledgeable of the importance of iodinated salt in their diet and if they are this is not necessarily widely available. Further, data about iodine sufficiency in pregnant women are scarce worldwide and many countries report urinary iodine values lower than the recommended (19,29), as we also found in this study. The data presented here contributes to the discussion on whether thyroid function should be monitored before and/or throughout pregnancy, on which thyroid function parameter is most appropriate for such screening (4,11–16,30), and on the need to establish a cutoff for identifying hypothyroxinemia/hypothyroidism in pregnant women that is distinct from the cutoff that defines normality in the general population (24). When considering hypothyroxinemia, our results confirm other findings (5,7,8,25) in which, using the current reference range for TSH, measurement of TSH alone is not sufficient. Screening is, however, controversial, because scientific and clinical societies do not agree on whether the available data are sufficient to provide such recommendations (13–15). Although severe iodine insufficiency is well recognized as the second major cause of preventable mental retardation, after starvation (1,5,10), an increasing body of evidence suggests that mild iodine insufficiency prevents children from fully achieving their intellectual potential (5,7,8). Identification of hypothyroxinemia during pregnancy, particularly in the first trimester, when fetal thyroid hormones rely exclusively on the mother's, is important because it has been shown to result in poorer pregnancy outcome (5,14), negatively impacting the psychomotor development and intelligence coefficient of the progeny (1,5–8). For these reasons, the WHO and several investigators are recommending supplementation of iodine before and during pregnancy, as well as the screening of thyroid function before or in the beginning of pregnancy (14,17,18). In conclusion, we recommend that a general policy on salt iodization and iodine supplementation during pregnancy and lactation be implemented, and that when no gestation-specific reference values are established, care should be taken when analyzing the results of thyroid hormone tests in iodine-insufficient populations.

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Disclosure Statement

The authors declare that no competing financial interests exist.

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