

Iodine status among pregnant women after mandatory salt iodisation

İ. Anaforoğlu^{1*}, E. Algün¹, Ö. İnceçayır¹, M. Topbaş² and M. F. Erdoğan³

¹Department of Endocrinology and Metabolism, Trabzon Kanuni Education and Research Hospital, 61290 Trabzon, Turkey

²Department of Public Health, Faculty of Medicine, Karadeniz Technical University, 61080 Trabzon, Turkey

³Department of Endocrinology and Metabolism, Faculty of Medicine, Ankara University, 06100 Ankara, Turkey

(Submitted 21 April 2015 – Final revision received 8 October 2015 – Accepted 19 October 2015 – First published online 24 November 2015)

Abstract

I is essential for thyroid hormone synthesis and neurological development. Various changes occur in thyroid hormone metabolism during pregnancy and I requirements increase significantly. The purpose of this study was to investigate I status among pregnant women in Trabzon, formerly a severely I-deficient area but shown to have become I sufficient following mandatory iodisation of table salt based on monitoring studies among school-age children (SAC) in the area. A total of 864 healthy pregnant women with a median age of 28 (25th–75th percentile 17–47) years participated in the study. None of them were using I-containing supplement. All of them were screened for use of iodised salt, obstetric history, thyroid function tests and urinary I concentrations (UIC), and thyroid ultrasonography was performed. Median UIC was 102 (25th–75th percentile = 62–143) µg/l. Median UIC of the patients according to trimesters were 122 µg/l at the 1st, 97 µg/l at the 2nd and 87 µg/l at the 3rd trimester. UIC in the 1st trimester was higher compared with the 2nd and 3rd trimesters ($P < 0.017$). Nodules were present in 17.7% of women ($n = 153$). The rate of iodised salt usage among pregnant women was 90.7%. Our study demonstrates that, although the I status among SAC has been rectified, I deficiency (ID) is still prevalent among pregnant women. Current knowledge is in favour of I supplementation in this group. Until the effects of maternal I supplementation in mild ID have been clarified by large-scale prospective controlled trials, pregnant women living in borderline deficient and I-sufficient areas, such as Trabzon city, should receive 100–200 µg/d of I-containing supplements in addition to iodised salt.

Key words: Thyroid: Pregnancy: Iodine: Iodine deficiency: Iodine supplementation

I deficiency (ID) is recognised as a public health problem across the world. Severe ID throughout pregnancy increases the risk of mental retardation, may harm brain development and intelligence development. ID may also lead to goitre formation during pregnancy^(1,2).

I requirements increase during pregnancy and breast-feeding. The fetus is highly dependent on maternal thyroxine sources for its neurodevelopment until its own thyroid gland begins to function. After formation of the fetal thyroid gland, fetal thyroid hormone production increases, contributing to increased maternal I requirements. As the maternal glomerular filtration rate increases from the beginning of early pregnancy, iodide filtration increases, resulting in a reduced circulating pool of plasma I. Thyroid hormone demand thus increases from the early weeks of gestation, and this necessitates an adequate I supply^(1–3).

The WHO recommends a daily I intake of 150 µg/d for non-pregnant women and 250 µg/d for pregnant and lactating women⁽⁴⁾. Low median urinary I concentration (UIC) values have been reported in the last few years in pregnant American women⁽⁵⁾. The American Thyroid Association, the Endocrine

Society and the Neurobehavioral Teratology Society have recommended that women planning a pregnancy or who are pregnant or lactating should receive 150 µg/d I-containing supplements^(6–8). However, data from the National Health and Nutrition Examination Survey (2001–2006) showed that only a small percentage (20%) of pregnant American women routinely took an I-containing supplement⁽⁹⁾. Routine I supplementation is also recommended in Europe, but this is not systematically applied in many European countries⁽¹⁰⁾.

Goitre prevalence below 5% in a population indicates that salt iodisation in that region is sufficient⁽⁴⁾. Goitre regression usually lags behind urinary I increment for about 1 or more years; the measurement of UIC is recommended in order to demonstrate the success of such programmes⁽⁴⁾. Although many urine samples (twelve samples or more) are required for individual measurements, studies have reported that one sample is sufficient for population surveys. In all, 500 spot urine samples are reported to be adequate to describe a population's median I excretion with approximately 5% precision⁽¹¹⁾. This is clarified in a subsequent study by the same group. They state that the median I concentration of spot urinary samples

Abbreviations: ID, iodine deficiency; SAC, school-age children; TSH, thyroid-stimulating hormone; UIC, urinary iodine concentrations.

* **Corresponding author:** İ. Anaforoğlu, fax +90 462 230 2307, email ianaforglu@hotmail.com

obtained from at least 500 subjects is a reliable measure of the I intake of the population⁽¹²⁾.

Erdoğan *et al.*⁽¹³⁾ identified ID in various regions of Turkey by conducting surveys among school-age children (SAC) between 1997 and 1999. Monitoring studies performed after the mandatory iodisation of table salt in 2007 showed that ID had been eradicated in most regions of the country⁽¹⁴⁾. Trabzon was defined as an I-sufficient area in 2007 with a median UIC of 145 µg/l among SAC⁽¹⁵⁾.

The number of studies regarding I status in pregnant women is limited. Studies carried out in Turkey to date have been mainly local with small samples. The purposes of this study were to investigate I status in pregnant women in Trabzon, a severely I-deficient area in 1997, which is now reported to be I sufficient, according to SAC I surveys conducted in 2007, following mandatory iodisation of table salt in 1999, and to propose relevant I supplementation for pregnant women who are prone to ID^(13,14).

Methods

The present study was carried out in Trabzon province, which has a pregnant women population of approximately 4500/year, between September 2011 and September 2012. The sample size was calculated using the formula $n = (DEFF \times Np(1-p)) / ((d^2/Z^2 - a/2 \times (N-1) + p \times (1-p)))$, where the number calculated was 843, the number planned was 1000 and the number included was 864 (DEFF = design effect = 1; $p = 50\%$; $d = 0.05$; $z = 1.96$; $N = 4500$; $\alpha = 0.05$; power = 99%)⁽¹⁶⁾. Lists of pregnant women registered with family health physicians were obtained, and 1000 women were selected by systematic sampling. Their names were given to family health physicians and these women were then invited to participate in the study. Registered pregnant women were referred by family health physicians. Family health clinics were visited in cases where pregnant women were unable to attend our clinic. Mean age of the pregnant women was 28 (25th–75th percentile 17–47) years; 29.5% were in the 1st trimester, 35.5% were in the 2nd and 35% were in the 3rd trimester ($n = 255, 307$ and 302 , respectively). Women in weeks 1–13 of gestation represented the 1st trimester, women in weeks 14–27 the 2nd trimester and women in weeks 27–40 represented the 3rd trimester. None of the pregnant women were using I-containing supplements. Fasting blood and urine samples were collected, and levels of thyroid-stimulating hormone (TSH), free triiodothyronine (T3), free thyroxine (T4), anti-thyroglobulin (anti-Tg) and anti-thyroid peroxidase (anti-TPO) were determined from the serum. Immunochemiluminescent assays performed on an automated analyzer (Advia Centaur XP; Siemens⁽¹⁷⁾) were used to measure levels of TSH, free T3, free T4, anti-Tg and anti-TPO. Thyroid ultrasonography (TUSG) was performed on 820 women. Ultrasonography (USG) was performed using a Hitachi 12 MHz USG device (Hitachi) on the 247 pregnant women who attended the hospital and using a portable Chison 7.5 MHz USG device (Chison) for the 573 women examined at family health clinics, by the same observers on all occasions (I. A., O. I.). The inter-observer variability among the two sonographers was

assessed in twenty patients and it was <15%. Urine samples collected at family health clinics were transferred to the hospital daily. Samples collected at family health clinics and at the hospital were all stored in de-iodised I tubes at -40°C . A single spot urine sample was collected in the morning (between 09.00 and 12.00 hours) from each participant. UIC was measured using the spectrophotometric method described by Sandell & Kolthoff⁽¹⁸⁾. The I laboratory is a part of the Ensuring the Quality of Iodine Procedures (EQUIP) programme conducted by the Center for Disease Control (CDC), USA, since 2009. The I laboratory is externally controlled by the 2013–2014 EQUIP programme, three times per year, and our average success as decided by the CDC is 75–80%/year. A standard questionnaire was administered by either a training nurse or the relevant physician (I. A.). Demographic data, monthly income, iodised salt usage (i.e. consumption without cooking) and storage conditions (protecting the salt against humidity or light) were recorded. Pregnant women with a known history of any thyroid disease (nodular goitre, thyroiditis, hypothyroidism, hyperthyroidism, history of any thyroid operation or use of any medication for any thyroid disease) were excluded.

Statistical Package for the Social Sciences (SPSS) software (SPSS version 16.0; SPSS Inc.) was used for the statistical analyses. Standard descriptive analysis was used. Data normality was assessed using the Kolmogorov–Smirnov test and ANOVA (Bonferroni test as *post hoc*) for normally distributed data and the Mann–Whitney *U* test and the Kruskal–Wallis test (Mann–Whitney *U* test with Bonferroni correction as *post hoc*) for non-normally distributed data. Results are shown as arithmetic means and standard deviations for normally distributed data and medians and 25th–75th percentile for non-normally distributed data. $P < 0.05$ was considered to be significant.

All women invited to take part were provided with written information about the study, and written consent was obtained from all the participants. The study was approved by the local ethics committee of Trabzon Kanuni Education and Research Hospital (Approval No. 27.12.2010-8/2010).

Results

The median UIC was 102 (25th–75th percentile = 62–143) µg/l. Table 1 summarises the results of UIC in pregnant women including distribution of UIC by trimesters. UIC was >150 µg/l in only 191/864 (22.1%) women and <150 µg/l in 673/864 (77.9%) women. UIC in the 1st trimester was higher compared with the 2nd and 3rd trimesters. The median UIC was 122 µg/l at the 1st, 97 µg/l at the 2nd and 87 µg/l at the 3rd trimester ($P < 0.017$) (Table 1). Thyroid function tests in terms of trimester are given in Table 2. Mean TSH values (reference range: 0.35–5.5 µIU/ml⁽¹⁸⁾) were 1.7 (SD 2.9), 1.7 (SD 1.2) and 2.1 (SD 1.31) µIU/ml, respectively, in the 1st, 2nd and 3rd trimesters ($P < 0.001$; for all trimesters). Free T4 and T3 values decreased significantly during pregnancy ($P < 0.001$; for all trimesters).

The mean thyroid volume was 12.9 (SD 7.5) ml. Of the study population, 14.8% ($n = 121$) had thyroid volumes exceeding 18 ml. There was no correlation between thyroid volume and trimester.

Table 1. Urinary iodine concentrations (UIC)* of pregnant women according to trimesters (Medians and 25th–75th percentiles)

Trimesters	Percentile			Frequency of distribution					
	50th (median UIC†)	25th	75th	<150 %	n	150–250 %	n	≥250 %	n
1st trimester (n 255)	122	77	150	71	181	18.4	47	10.6	27
2nd trimester (n 307)	97	57	140	79.2	243	16.3	50	4.6	14
3rd trimester (n 302)	87	54	134	82.5	249	12.3	37	5.3	16
n 864/%	102	62	143	77.9	673	15.5	134	6.6	57
	<i>P</i> = 0.017‡								

* Morning spot urine samples.

† The median UIC of the 1st trimester is higher than the median UIC of the 2nd and 3rd trimesters.

‡ The difference is derived from the 1st trimester (*P* = 0.017).

Table 2. Thyroid function tests of pregnant women with regard to trimesters (Mean values and standard deviations)

Trimesters	TSH (0.35–5.5 µIU/ml)*		FT3 (1.5–2.7 pmol/l)*		FT4 (6.9–13.7 pmol/l)*	
	Mean	SD	Mean	SD	Mean	SD
1st trimester (n 255)	1.7	2.9	2.2	0.6	9.5	2.4
2nd trimester (n 307)	1.7	1.2	1.8	0.3	7.9	1.2
3rd trimester (n 302)	2.1	1.3	1.8	0.2	7.3	1.2
<i>P</i> †	<0.001		<0.001		<0.001	
n 864	1.9	1.9	1.9	0.4	8.1	1.9

TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine.

* Normal reference range; not specific for trimesters.

† ANOVA.

Thyroid nodules were present in 17.7 % of pregnant women (*n* 153), and thyroid autoantibody positivity was observed in 14.5 % (*n* 119). Thyroid autoantibody positivity was significantly higher in those with heterogeneous thyroid parenchyma (*n* 186, 22.7 %) (*P* < 0.001) reported at TUSG.

A total of 248 subjects (28.4 %) stated that they were aware of the importance of ID and its consequences. Of the 864 subjects, 784 (90.7 %) reported that they were using iodised salt, whereas thirty subjects (3.5 %) reported that they were not using it, and others (5.8 %) stated that they did not know about the importance of using iodised salt. When asked whether they stored or added the salt to food appropriately – that is, adding towards the end of the cooking process – 303 (64.9 %) subjects were found to be using it inappropriately by adding iodised salt at the beginning of the cooking process. In terms of storage, 216 (25 %) subjects used appropriate containers, and UIC levels were not different when stratified by the use of iodised salt, history of I-rich diet, awareness of the relationship between I and pregnancy, education level, monthly income level or history of thyroid disease in the family (Table 3) (*P* > 0.5).

Discussion

UIC measurement in spot urine samples is recommended for determination of I status among SAC by the WHO and International Council for Control of Iodine Deficiency Disorders (ICCIDD) for population I nutrition monitoring. It has also been reported to be useful for pregnant and lactating women⁽⁴⁾.

In order for a population to be considered I sufficient, the median UIC of SAC in that community must be >100 µg/l.

Median UIC of 50–99 µg/l indicates mild, 20–49 µg/l indicates moderate and <20 µg/l indicates severe ID⁽⁴⁾. However, pregnant women have greater I requirements for the reasons discussed above. For pregnant women, median UIC >150 µg/l is insufficient, and it should be between 150 and 249 µg/l for this population⁽⁴⁾.

I status of SAC in Trabzon was reported to be severely deficient (median UIC of 14 µg/l) in a national survey conducted between 1997 and 1999⁽¹³⁾. Following the mandatory iodisation of table salt with 25–40 mg/kg KIO₃ or 50–70 mg/kg KI, monitoring studies in 2002 and 2007 determined median UIC of 113 and 145 µg/l, respectively, among SAC in Trabzon, showing that the province was I sufficient^(14,15).

These nationwide monitoring studies of SAC by Erdoğan *et al.*^(13,14,19) showed a significant correction of ID, especially in urban areas. However, previous studies among the pregnant population were limited and involved small sample sizes^(20–26). These small-sized studies among pregnant women from different regions of Turkey reported median UIC between 77.4 and 149.7 µg/l and that 49.6–100 % of pregnant women were at risk of ID^(20–26). Although the median UIC of SAC from most of these areas was sufficient or mildly deficient, ID was still a common problem among pregnant women^(20–26).

Current data from the Trabzon provincial centre, formerly endemic but currently an I-sufficient region in the light of SAC surveys, show that the population median UIC is below the WHO threshold of adequacy in all three trimesters of pregnancy. The use of iodised salt in the region among the pregnant population needs additional I support from the 1st trimester onwards. Large-scale monitoring studies recently conducted

Table 3. Analysis of urinary iodine concentrations according to related factors (Medians and 25th–75th percentiles)

	Median	Percentile	
		25th	75th
Awareness of importance of I			
Aware of (<i>n</i> 245)	101	60	144
Not (<i>n</i> 619)	102	62	143
<i>P</i> *		0.958	
Iodised salt			
Using (<i>n</i> 773)	101	61.5	143
Not (<i>n</i> 91)	108.5	75	146.5
<i>P</i> *		0.592	
Education			
Primary school (<i>n</i> 289)	100	62.3	144
Secondary school (<i>n</i> 154)	111.5	73	150
High school (<i>n</i> 286)	101	57	140
University (<i>n</i> 135)	97	58	138.5
<i>P</i> †		0.236	
Monthly income			
<1000 (<i>n</i> 398)	106	66	144
1000–1500 (<i>n</i> 210)	100	52	140
>1500 (<i>n</i> 256)	97	60	145
<i>P</i> †		0.298	

* Mann–Whitney *U* test.

† Kruskal–Wallis analysis.

among pregnant women from the cities of Ankara and İstanbul also support our results (A Aktaş, Ü Aydın, Bİ Aydoğan, K Erkenekli, G Koç, Z Berberoğlu, Y Aral, MF Erdoğan, unpublished results, and E Oral, AS Açıkgöz, B Aydoğan, Bİ Aydoğan, HÇ Acioğlu, GA İlhan, B Dane, A Özel, H Erenel, B Tandoğan, E Çakar, H İşçi, B Kayan, H Aslan, A Ekiz, S Sancak, A Çelik, T Yoldemir, Ö Uzun, MF Erdoğan, unpublished results). The results of the 1st study performed among 312 pregnant women showed that 76, 82 and 91 % of women from Ankara – a borderline I-sufficient city⁽¹⁴⁾ – were I deficient during the 1st, 2nd and 3rd trimesters of pregnancy, respectively (A Aktaş, Ü Aydın & Bİ Aydoğan, unpublished results). Similarly, although İstanbul is described as an I-sufficient city in SAC surveys⁽¹⁴⁾, one multicentre study involving 3543 pregnant women from nine different gynaecology and obstetrics clinics from the city of İstanbul, conducted in 2013, showed that 90.7 % of pregnant women were I deficient during pregnancy (E Oral, AS Açıkgöz & B Dane, unpublished results). UIC measured from single samples from pregnant women was not associated with history of stillbirth, congenital anomalies or spontaneous abortus, in agreement with our study results (E Oral, AS Açıkgöz & B Dane, unpublished results).

The consequences of severe ID during pregnancy and lactation are well known, whereas studies concerning the effects of mild-to-moderate ID are inconsistent⁽²⁷⁾. A recent observational study of 1040 mothers and their children showed that even mild ID *in utero* is linked to lower intelligence quotient and suboptimal reading ability in 8-year-old children⁽²⁸⁾. Children's scores worsened when the deficient group (UIC < 150 µg/l) was subdivided into groups with UIC between 50 and 150 µg/l and those with UIC < 50 µg/l⁽²⁸⁾. Similarly, a study from Tasmania showed that children whose mothers had UIC < 150 µg/l during pregnancy scored 10 % lower in spelling, 7.6 % in grammar and

5.7 % in English literacy performance compared with children whose mothers had UIC > 150 µg/l⁽²⁹⁾. Another study from the Netherlands showed that low maternal UIC during pregnancy is associated with impaired executive functioning in children⁽³⁰⁾.

Among intervention studies examining the impact of maternal I supplementation on the neurodevelopment of children, Velasco *et al.*⁽³¹⁾ observed that children of I-supplemented mothers exhibited better behavioural and psychomotor performance than those of untreated mothers. In a study of development quotient from Spain, delayed neurobehavioural performance was reported to be higher in children whose mothers did not receive supplementation from early pregnancy⁽³²⁾.

Murcia *et al.*⁽³³⁾ reported lower psychomotor development indices among infants whose mothers received >150 µg/d of I supplementation than those of mothers receiving <100 µg/d. In contrast, Santiago *et al.*⁽³⁴⁾ determined no difference in terms of mental development or psychomotor scales, between mothers using iodised salt or I supplementation. A recently published study from the Netherlands also detected no association between maternal low UIC and children's cognition. In that study, the authors stated that the research was not powerful enough to detect a significant association because the number of women with ID was very low⁽³⁵⁾. Finally, a large meta-analysis investigating the effects of maternal I supplementation concluded that large-scale controlled, prospective trials are needed to clarify the situation⁽³⁶⁾.

We found no difference when our results were stratified by the use of iodised salt, awareness of the importance of I in pregnancy, education level or monthly income. This may be due to the use of spot and single urine examples, as this was a population survey study. More samples per participant (e.g. ten to twelve independent urine samples per participant) could yield I status at the individual level. More participants, with only

single spot urine per participant, may not appreciably add to the interpretation of population median values as conducted in the present study and would not increase the interpretive value for individuals. As described in two different reviews, analyses of as few as two independent urine samples per participant, followed by appropriate statistical modelling to remove within-individual variation, could yield fully interpretable population distributions of habitual UIC, which could be effectively used to evaluate proportion of the study below a threshold^(37,38).

ID levels as well as TSH levels increased by trimester in our study. Median UIC were lower in the 2nd and 3rd trimesters. Free T3 and free T4 levels in the serum decreased parallel to the increase in TSH and decrease in median UIC. These findings may partly be explained by physiological changes in thyroid hormone metabolism in pregnancy (i.e. dilution or an increasing glomerular filtration rate and increasing I demand), as well as the worsening of I status during the trimesters⁽¹⁻⁴⁾.

In terms of thyroid nodularity (the prevalence of nodule in the general population), the 35.2% prevalence rate reported by a prevalence study performed in our region by Koçak *et al.*⁽³⁹⁾ was considerably higher than that in our population. However, the prevalence of nodules in the young population (20–29 years) in that study was 12.5%, rising to 38.4% in individuals aged over 70 years⁽³⁹⁾. Similarly, overall goitre prevalence was higher than that in our population (14.8 *v.* 28.4%), and there was a significant increase in volume with advancing age. In this formerly I-deficient area, prevalence of goitre was 12.5% in the 20–29 years age group and 38.4% in the over 70 years age group⁽³⁹⁾.

Iodised salt stored in open containers may lose 50–100% of its I content due to humidity and other factors when KI is used for iodisation⁽⁴⁰⁾. Similarly, Wang *et al.*⁽⁴¹⁾ reported that iodised salt loses 2–63% of its I content when salt is added before or early during cooking. In all, 25% of the women in our study stored iodised salt appropriately, and 65% added iodised salt properly after cooking. Fortunately KIO₃, which is much more stable than KI, has been used for salt iodisation in Turkey since 2010⁽⁴²⁾.

In conclusion, despite the global I supplementation programme, which has improved I status worldwide, ID is still a serious health problem, especially among pregnant women. Current knowledge is in favour of I supplementation in this risk group. Until the effects of maternal I supplementation, in mild ID, are clarified by large-scale prospective controlled trials, pregnant women living in borderline deficient and I-sufficient areas, such as Trabzon city, should receive 100–200 µg/d I-containing supplements in addition to iodised salt, depending on the severity of deficiency among SAC.

Acknowledgements

The authors thank the family physicians for providing lists of registered pregnant women and inviting them to participate in the study. The authors also thank the nurse Ebru Güneykaya and the secretaries Hatice Konaş and Sevgi Özer for their secretarial assistance.

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

The authors' contributions are as follows: I. A., E. A. and M. F. E. designed the study; I. A. and O. I. collected data;

I. A. drafted the paper; I. A. and M. F. E. wrote the manuscript; and I. A., M. F. E. and M. T. were responsible for data analyses and data interpretation. M. F. E. critically read and revised the paper. All the authors read and approved the final version of the manuscript.

The authors declare that there are no conflicts of interest.

References

- Lazarus JH (2011) Thyroid function in pregnancy. *Br Med Bull* **97**, 137–148.
- Burrow GN, Fisher DA & Larsen PR (1994) Maternal and thyroid function. *N Engl J Med* **331**, 1072.
- Leung AM, Pearce EN & Braverman LE (2011) Iodine nutrition in pregnancy and lactation. *Endocrinol Metab Clin North Am* **40**, 765–777.
- World Health Organization, United Nations International Children's Emergency Fund & ICCIDD (2007) *Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination – A Guide Programme Managers*, 3rd ed. Geneva: WHO.
- Stagnaro-Green A, Abalovich M, Alexander E, *et al.* (2011) Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* **21**, 1081–1125.
- Caldwell KL, Pan Y, Mortensen ME, *et al.* (2013) Iodine status in pregnant women in the National Children's Study and in U.S. women (15–44 years), National Health and Nutrition Examination Survey 2005–2010. *Thyroid* **23**, 927–993.
- De Groot L, Abalovich M, Alexander EK, *et al.* (2012) Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* **97**, 2543–2565.
- Obican SG, Jahnke GD, Soldin OP, *et al.* (2012) Teratology public affairs committee position paper: iodine deficiency in pregnancy. *Birth Defects Res A Clin Mol Teratol* **94**, 677–682.
- Gregory CO, Serdula MK & Sullivan KM (2009) Use of supplements with and without iodine in women of childbearing age in the United States. *Thyroid* **19**, 1019–1020.
- Zimmermann M & Delange F (2004) Iodine supplementation of pregnant women in Europe: a review and recommendations. *Eur J Clin Nutr* **58**, 979–984.
- Andersen S, Karmisholt J, Pedersen KM, *et al.* (2008) Reliability of studies of iodine intake and recommendations for number of samples in groups and individuals. *Br J Nutr* **99**, 813–818.
- Vejbjerg P, Knudsen N, Perrild H, *et al.* (2009) Estimation of iodine intake from various urinary iodine measurements in population studies. *Thyroid* **19**, 1281–1286.
- Erdoğan G, Erdogan MF, Emral R, *et al.* (2002) Iodine status and goiter prevalence in Turkey before mandatory iodination. *J Endocrinol Invest* **25**, 224–228.
- Erdogan MF, Ağbaht K, Altınsu T, *et al.* (2009) Current iodine status in Turkey. *J Endocrinol Invest* **32**, 617–622.
- Erdoğan MF, Demir O, Emral R, *et al.* (2009) More than a decade of iodine prophylaxis is needed to eradicate goiter among school age children in a moderately iodine-deficient region. *Thyroid* **19**, 265–268.
- Dean AG, Sullivan KM & Soe MM (2015) OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com
- Owen WE, Gantzer ML, Lyons JM, *et al.* (2011) Functional sensitivity of seven automated thyroid stimulating hormone immunoassays. *Clin Chim Acta* **412**, 2336–2339.
- Sandell EB & Kolthoff IM (1937) Micro determination of iodine by a catalytic method. *Microchem Acta* **1**, 9–25.

19. Erdogan G, Erdogan MF, Delange F, *et al.* (2000) Moderate to severe iodine deficiency in three endemic goitre areas from the Black Sea region and the capital of Turkey. *Eur J Epidemiol* **16**, 1131–1134.
20. Mocan MZ, Erem C, Telatar M, *et al.* (1995) Urinary iodine levels in pregnant women with and without goiter in the Eastern Black Sea part of Turkey. *Trace Elem Electroly* **12**, 195–197.
21. Egri M, Ercan C & Karaoglu L (2008) Iodine deficiency in pregnant women in Eastern Turkey (Malatya Province): 7 years after the introduction of mandatory table salt iodization. *Public Health Nutr* **12**, 849–852.
22. Kışlal F, Çetinkaya S, Dilmel U, *et al.* (2010) Cord blood thyroid-stimulating hormone and free T4 levels in Turkish neonates: is iodine deficiency still a continuing problem? *Pediatr Intern* **52**, 762–768.
23. Köksal E & Pekcan G (2007) Urinary iodine excretion in pregnant women and their outcome. Micronutrient Forum, 16–18 April 2007. İstanbul: Abstract Book. http://www.micronutrientforum.org/meeting2007/MN%20Forum%20Program%20Part%20II_Abstracts.pdf
24. Çetinkaya K, İngeç M, Çetinkaya S, *et al.* (2012) Iodine deficiency in pregnancy and in women of reproductive age in Erzurum. *Turk J Med Sci* **42**, 675–680.
25. Kut A, GURSOY A, ŞENBAYRAM S, *et al.* (2010) Iodine intake is still inadequate among pregnant women eight years after mandatory iodination of salt in Turkey. *J Endocrinol Invest* **33**, 461–464.
26. Kutlu AO & Kara C (2012) Iodine deficiency in pregnant women in the apparently iodine-sufficient capital city of Turkey. *Clin Endocrinol (Oxf)* **77**, 615–620.
27. Zimmermann MB, Jooste PL & Pandav CS (2008) Iodine deficiency disorders. *Lancet* **372**, 1251–1262.
28. Bath SC, Steer CD, Golding J, *et al.* (2013) Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet* **27**, 331–337.
29. Hynes KL, Otahal P & Hay I (2013) Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. *J Clin Endocrinol Metab* **98**, 1954–1962.
30. van Mil NH, Tiemeier H, Bongers-Schokking JJ, *et al.* (2012) Low urinary iodine excretion during early pregnancy is associated with alterations in executive functioning in children. *J Nutr* **142**, 2167–2174.
31. Velasco I, Carreira M, Santiago P, *et al.* (2009) Effect of iodine prophylaxis during pregnancy on neurocognitive development of children during the first two years of life. *J Clin Endocrinol Metab* **94**, 3234–3241.
32. Berbel P, Mestre JL, Santamaria A, *et al.* (2009) Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. *Thyroid* **19**, 511–519.
33. Murcia M, Rebagliato M, Iniguez C, *et al.* (2011) Effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 year of age. *Am J Epidemiol* **173**, 804–812.
34. Santiago P, Velasco I, Muela JA, *et al.* (2013) Infant neurocognitive development is independent of the use of iodised salt or iodine supplements given during pregnancy. *Br J Nutr* **114**, 831–839.
35. Ghassabian A, Steenweg-de GJ, Peeters RP, *et al.* (2014) Maternal urinary iodine concentration in pregnancy and children's cognition: results from a population-based birth cohort in an iodine-sufficient area. *BMJ Open* **12**, 4.
36. Taylor PN, Okosieme OE, Dayan CM, *et al.* (2013) Therapy of endocrine disease: impact of iodine supplementation in mild-to-moderate iodine deficiency: systematic review and meta-analysis. *Eur J Endocrinol* **22**, R1–R15.
37. Zimmermann MB & Andersson M (2012) Assessment of iodine nutrition in populations: past, present and future. *Nutr Rev* **70**, 553–570.
38. Rohner F, Zimmermann M, Jooste P, *et al.* (2014) Biomarkers of nutrition for development-iodine review. *J Nutr* **144**, 1322S–1342S.
39. Koçak M, Erem C, Deger O, *et al.* (2014) Current prevalence of goiter determined by ultrasonography and associated risk factors in a formerly iodine deficient area of Turkey. *Endocrine* **47**, 290–298.
40. Diosady LL, Alberti JO, Venkatesh MVG, *et al.* (1997) Stability of iodine in iodized salt used for correction of iodine-deficiency disorders. *Food Nutr Bull* **18**, 388–439.
41. Wang GY, Zhou RH, Wang Z, *et al.* (1999) Effects of storage and cooking on the iodine content in iodized salt and study on monitoring iodine content in iodized salt. *Biomed Environ Sci* **12**, 1–9.
42. Türk Gıda Kodeksi Tuz Tebliği (Legislation of Turkish Food Codex of Salt) (Tebliğ No: 2013/48). <http://www.mevzuat.gov.tr/Metin.aspx?MevzuatKod=9.5.18730&MevzuatIliski=0&sourceXmlSearch=tuz> (accessed September 2015).

