IODINE STATUS IN PREGNANT WOMEN AFTER A DECADE OF UNIVERSAL SALT IODIZATION IN ROMANIA

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Abstract

Objective. To assess iodine status (median urinary iodine concentration) in 118 pregnant women during the third trimester from endemic or non-endemic areas, a decade after implementation of Universal Salt Iodization in Romania.

Subjects and methods. One hundred and eighteen pregnant women in the third trimester were included in the study group (age range: 16 – 46 years, mean age: 28.78 years). Median urinary iodine concentration (UIC) and body mass index (BMI) were evaluated. Data regarding region of provenance, smoking habits during pregnancy, education level, iodized salt intake, bread intake, iodine supplements, comorbidities (iron deficiency anemia) and birth weight were assessed. Morning urine was collected to measure median UIC. The study was approved by the Local Ethics Committee.

Results. Median UIC in the study group was 206 mcg/L, reflecting iodine sufficiency during pregnancy. There is a statistically significant difference between pregnant women with and without iodine supplements from rural areas (281.5 *versus* 196.1 mcg/L, respectively, $p=0.023$). In the subgroup without iodine supplementation, there was a significant difference between overweight and obese subjects *vs.* normal weight subjects (232.5 *versus* 194 mcg/L, $p=0.012$). Only in the subgroup with a daily intake of less than 5 slices of bread (usually containing iodized salt) we found significant differences between those with and without iodine supplements (245.2 *versus* 128.3 mcg/L). Iron deficiency anemia was found in 29.66% and 19.49% were current smokers during pregnancy.

Conclusions. Median UIC in the study group was 206 mcg/L, reflecting iodine sufficiency during pregnancy. The difference between the subgroup with iodine supplements and the subgroup without iodine supplements was not statistically significant, probably due to the excessive consumption of bread and other bakery products which is traditional in Romania.

Key words: iodine deficiency, universal salt iodization, pregnant women, iodine supplementation.

INTRODUCTION

Maternal iodine deficiency during pregnancy is associated with impaired child cognitive function (1). Even mild to moderate iodine deficiency during pregnancy can have long-term adverse effects on child cognitive function (2). Every child has the right to an adequate supply of iodine to ensure his (or her) normal development (3). As a result of remarkable efforts in the past two and a half decades, the latest global estimate of iodine nutrition looks more optimistic than ever. The number of iodine deficient countries in the world has decreased from 54 in 2003 to 32 in 2011 (4). Universal salt iodization (USI) was promoted at the World Summit for Children (New York, 1990), as the main strategy for eliminating iodine deficiency. In Romania, the law regarding USI was implemented in January 2003 (HG 568) and allows a continuous iodine prophylaxis (5, 6). Programs against iodine deficiency disorders (IDD) had clear political appeal because its human, economic and social consequences could be averted by a low-cost intervention, Universal Salt Iodization (7). Different aspects of this topic (IDD) have been published in our country (8-12). Endemic goiter occurred in different degrees throughout 2/3 of Romania territory, mainly in the Carpathian and sub-Carpathian areas (6). Iodine deficiency may occur also in industrialized countries, not only in developing countries. Mild iodine deficiency was revealed recently in the UK (13). Iodine deficiency is especially problematic in pregnant women, who have a higher iodine requirement (250 mcg per day) than non-pregnant women (150 mcg per day) (2). The European Thyroid Association has recommended that women who are pregnant, lactating or planning a pregnancy should ingest daily supplements containing 150 mcg iodine (14). Our study performed on a group of 102

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schoolchildren from two urban areas, a decade after implementation of universal salt iodization in Romania, revealed iodine sufficiency (median urinary iodine concentration was 175.2 mcg/L) (5). In a previous Romanian paper, median UIC was low and quite similar in pregnant women both before implementation (January 2003) of Universal Salt Iodization (52 mcg/L in 2001) and 2 years after the above mentioned implementation (55 mcg/L) (6). Consequently, these low values during pregnancy were considered an emergency problem that had to be solved as soon as possible (risk of irreversible mental retardation) (6). An increased prevalence of ADHD represents another risk related to iodine deficiency during pregnancy (15). In humans, most of the growth and development of the brain occur during fetal life and the first 3 postnatal months (16). According to a recent paper, Romania belongs to a group of nine European countries, with a suboptimal iodine status of pregnant women (4). Consequently, in this study we intend to evaluate iodine status in 118 pregnant women (during third trimester) after a decade of Universal Salt Iodization, with or without daily supplements containing 150 mcg iodine.

AIM

The study assessed iodine status (median urinary iodine concentration) in 118 pregnant women during third trimester from endemic (77 pregnant women) or non-endemic areas (41 pregnant women), a decade after implementation of Universal Salt Iodization in Romania. Results achieved were compared with iodine status in pregnant women before implementation of Universal Salt Iodization.

SUBJECTS AND METHODS

Pregnant women admitted for delivery in the Polizu Clinical Hospital of Obstetrics and Gynecology Bucharest, between February and October 2015, from different geographical regions of Romania, were consecutively recruited for this study.

One hundred and eighteen pregnant women in the third trimester of pregnancy, aged between 16 and 46 years old (mean age: 28.87 years), were included in the study.

Anthropometric measurements were made for all subjects (weight, height) when the urine was collected. Body mass index (BMI) was calculated by the formula $BMI = \text{weight (kg)} / (\text{height (m)})^2$. Overweight was defined as BMI between 25 and 29.9 kg/m² and

obesity as $BMI \geq 30 \text{ kg/m}^2$.

Data regarding region of provenance, smoking habits during pregnancy, education level, medication, iodized salt intake, bread intake, iodine supplements intake, comorbidities (iron deficiency anemia, hypothyroidism) and children's birth weight were assessed.

Iodine intake was evaluated by determining the median urinary iodine concentration (median UIC). Urine samples of morning urine were collected to measure urinary iodine concentration. The samples were then frozen at -20° C and sent for analysis at the Bucharest Institute for Mother and Child Care. Urinary iodine concentration (UIC) was determined by digestion with ammonium persulfate followed by Sandell – Kolthoff reaction. The values were expressed in mcg/L. The detection limits were 8.15 - 478.59 mcg/L, the standard deviation for repeatability was 2.09 mcg/L and for reproducibility 4.81 mcg/L.

According to (2), median UIC between 150 and 499 mcg/L reflects an adequate iodine status in pregnant women, values below 150 mcg/L indicate iodine deficiency, and values over 500 mcg/L suggest iodine excess. Severe iodine deficiency is revealed when median UIC is below 50 mcg/L. A median UIC between 50 – 149 mcg/L reflects a mild to moderate iodine deficiency during pregnancy. Very high UIC (> 700 mcg/L), found in 12 pregnant women, were considered indicative of iodine contamination and were excluded from the study.

The study was approved by the Local Ethics Committee. An informed consent from the subjects was obtained.

Statistical analysis of data was done using SPSS software. Statistical significance was expressed by a p value of less than 0.05. The Mann-Whitney test doubled by Hodges-Lehman test was used for non-normal data group's comparison.

RESULTS

All pregnant women included in the study group were in the third trimester of pregnancy and the great majority used iodized salt (99.15%). None of the subjects had hypothyroidism. Mean age of subjects was 28.87 years old (age range: 16 – 46 years). From the 118 pregnant women group 38.98% were from rural areas and 61.02% from urban areas, 65.25% were from endemic goiter areas and 34.75% from non-endemic areas. Moreover, 69.49% had a higher education degree and 30.51% had a medium education level.

Figure 1. Median UIC in pregnant women in relation with iodine supplements intake.

Legend: pw = pregnant women, UIC = urinary iodine concentration.

Figure 2. Median UIC in iodine deficient and iodine sufficient areas in relation to iodine supplements intake.

Legend: UIC = urinary iodine concentration.

Taking into account the fact that the great majority of pregnant women used iodized salt, we divided the subjects into two subgroups: with iodine supplements intake (58 subjects) and without iodine supplements intake (60 subjects). The iodine supplements contained 150 mcg iodine and were taken daily, only during the pregnancy.

Median UIC in the total number of samples was 206.8 mcg/L with ranges between 29.8 and 563.4 mcg/L, reflecting sufficient iodine intake, without statistically significant differences between the subgroups with and without iodine supplements ($p=0.243$) (Fig. 1). Median UIC below 150mcg/L reflecting insufficient iodine intake were present in 27.96% of subjects and levels below 50 mcg/L were found in 1.69% of subjects. An adequate iodine intake expressed by UIC between 150 and 249 mcg/L was

Figure 3. Median UIC of pregnant women according to BMI.

Legend: UIC = urinary iodine concentration, BMI = body mass index.

Figure 4. Median UIC (mcg/L) in the subgroups of pregnant women with and without iodine supplements intake in relation to bread intake.

Legend: UIC = urinary iodine concentration.

present in 36.44% of subjects and above requirements iodine intake (between 250 and 499 mcg/L) was found in 32.20% of subjects. Excessive iodine intake was revealed in 3.39% of pregnant women and the term “excessive” means in excess of the amount required to prevent and control iodine deficiency (Table 1).

The median UIC in the subgroup with iodine supplements was 213.5 mcg/L (range 33.9 - 546.8 mcg/L) and it was 205.7 mcg/L in the subgroup without iodine supplements (range 29.8 - 563.4 mcg/L (Table 1).

The median UIC in rural areas was 210.3 mcg/L and 206.6 mcg/L in urban areas, without statistically significant difference ($p=0.2$).

In the subgroup from urban areas there were no statistically significant differences between pregnant women with and without iodine supplements intake

Table 1. Urinary iodine concentration (UIC) in pregnant women included in the study

	Urinary iodine concentration (mcg/L)		
	Total group	Group with iodine supplements	Group without iodine supplements
No. of samples	118	58	60
Median	206.8	213.5	205.7
Range	29.8-563.4	33.9-546.8	29.8-563.4
No. of values >500 mcg/L	4 (3.39%)	3 (5.17%)	1 (1.66%)
No. of values 250-499 mcg/L	38 (32.20%)	22 (37.93%)	16 (26.6%)
No. of values 150-249 mcg/L	43 (36.44%)	18 (31.03%)	25 (41.66%)
No. of values <150 mcg/L	33 (27.96%)	15 (25.86%)	18 (30%)
No. of values < 50 mcg/L	2 (1.69%)	1 (1.72%)	1 (1.66%)

($p=1$). There is a statistically significant difference between pregnant women with and without iodine supplements from rural areas, median UIC being 281.5 mcg/L in pregnant women with iodine supplements and 196.1 mcg/L in those without iodine supplements ($p=0.023$).

From the total number of pregnant women, 77 were from endemic goiter areas and 41 from non-endemic areas.

There were no statistically significant differences between the known endemic and non-endemic regions for goiter. The median UIC in endemic areas was 214.5mcg/L and 200.3mcg/L in non-endemic areas ($p=0.968$).

There were no statistically significant differences between the subgroups with and without iodine supplements in iodine deficient areas ($p=0.534$) and iodine sufficient areas ($p=0.306$) (Fig. 2). In the subgroup without iodine supplements there were no statistically significant differences between the endemic and non-endemic regions for goiter ($p=0.968$) (Fig. 2).

The percentage of pregnant women with overweight and obesity was 29.66% and in 70.34% of pregnant women a normal body weight was found. There were no statistically significant differences between the median UIC of pregnant women with overweight and obesity and with normal weight ($p = 0.066$). There were also no statistically significant differences between obese pregnant women with and without iodine supplements intake ($p = 0.905$).

In the subgroup with iodine supplements there were no statistically significant differences between those with normal weight and those with overweight and obesity ($p = 0.565$). In the subgroup without iodine supplements, there was a statistically significant difference between overweight and obese pregnant women and normal weight pregnant women ($p = 0.012$) (Fig. 3).

The percentage of pregnant women with an intake of more than 5 slices of bread/day was 66.10% (bread is usually containing iodized salt). Bread is usually containing 1.05 - 1.55 g of iodized salt per 100g, a 20 g slice of one of the most used brands of bread containing on average 9.3 mcg of iodine. There were no statistically significant differences between pregnant women with an intake of more or less than 5 slices of bread/day ($p = 0.245$), the median UIC being 211.7mcg/L in the subgroup with more than 5 slices of bread/day intake and 197.1mcg/L in the subgroup with less than 5 slices of bread/day. Between those with and without iodine supplements, there were statistically significant differences only in the subgroup with an intake of less than 5 slices of bread/day ($p= 0.027$) (Fig. 4).

There is no correlation between obesity and bread intake in the studied group (correlation coefficient = 0.19).

The percentage of pregnant women with associated iron deficiency anemia in the studied group was 29.66. Regarding the subgroup of pregnant women with insufficient iodine intake (UIC < 150 mcg/L) there are no statistically significant differences between pregnant women with or without associated iron deficiency anemia ($p = 0.374$), regardless of iodine supplements intake.

From the study group (118 pregnant women), 19.49% reported current smoking during pregnancy. There were no differences regarding smoking habits and use of iodine supplements between those with higher and medium degree of education.

The average maternal age was 28.87 years. The median UIC in pregnant women with ages under 28 yrs was 205 mcg/L and 214.2 mcg/L in pregnant women with ages above 28 yrs without statistically significant differences ($p=0.515$). There were also no statistically significant differences between the pregnant women with and without iodine supplements both in the subgroup with ages under 28 yrs ($p = 0.835$) and in the

subgroup with ages above 28 yrs ($p = 0.157$).

We obtained data regarding birth weight of the children from only 55 women: 29 from the group with iodine supplements and 26 from the group without iodine supplements. Median birth weight in the group of women receiving iodine supplements during pregnancy was 3300g (range 2100 - 4035g, 5th and 97th percentile = 2400g and 3963.6g, respectively), and in the group without supplements was 3225g (range 2550 - 4070g, 5th and 97th percentile = 2650g and 4017.5g respectively), $p = 0.980$.

DISCUSSION

Iodine deficiency is especially problematic in pregnant women, who have a higher iodine requirement (250 mcg per day) than non-pregnant women (150 mcg per day) because they need to synthesize additional thyroid hormone to cover maternal and fetal needs, and pass iodine to the fetus for thyroid hormone production (2). Maternal iodine deficiency during pregnancy is associated with impaired child cognition (1). Neuro-intellectual outcomes in children appear to be more dependent on their mothers' nutritional iodine status than on maternal thyroid function (17).

Use of iodized salt by the food industry should be strongly encouraged since iodine supplements often do not reach poorer, less educated women (2). In our study group there were no differences regarding the use of iodine supplements between pregnant women with higher education degree *vs.* those with medium education level.

According to a recent paper, adequate iodine nutrition in pregnant women is shown by a median UIC between 150 and 499 mcg/L (2).

In a previous Romanian paper, median UIC was low (52 mcg/L in 2001) in pregnant women before implementation of Universal Salt Iodization in January 2003, representing a risk of mental retardation (6). In 2005, median UIC in Romanian pregnant women was still low (71.7 mcg/L) (8). Median UIC in our study group was 206 mcg/L, reflecting iodine sufficiency during pregnancy a decade after the Universal Salt Iodization. In our study group an adequate iodine status (between 150 and 499 mcg/L) (2) was found in more than two-thirds (68.64%) of pregnant women, iodine deficiency (median UIC < 150 mcg/L) was revealed in 27.96%.

In our study group, vulnerabilities during fetal brain development, in pregnant women without iodine supplements (being at risk for borderline or decreased iodine intake) are represented by:

1. Rural areas (38.98%) – in pregnant women without iodine supplementation, median UIC was significantly lower *vs.* pregnant women with iodine supplementation (196.1 mcg/L *vs.* 281 mcg/L).

2. Normal body weight (70.34%) without iodine supplements represents another vulnerability (risk factor).

3. Iron deficiency anemia was found in 29.66% during pregnant women. Iron is crucial to early neurodevelopment (19). Iron deficiency anemia during pregnancy may increase the risk of autism (20). Both iodine and iron requirements are increased during pregnancy. Iron deficiency anemia reduces thyroid peroxidase activity in rats (21), contributing to hypothyroxinemia. Thyroid peroxidase is a heme-dependent enzyme and each heme contains an atom of iron.

4. Cigarette smoking was revealed in 19.49% during pregnant women. Cigarette smoking is a major source of thiocyanate in humans; thiocyanate levels were high in serum from smoking mothers and their neonatal infants (22). Thiocyanate inhibits competitively the function of the sodium-iodide symporter (NIS), which is the main thyroidal iodide transporter; NIS is also present in tissues other than the thyroid, such as the lactating mammary gland and the placenta (23). Smoking was associated with reduced iodine content in breast milk (smokers 26 mcg/L *vs.* 53.8 mcg/L in nonsmokers) (22). Smoking during breastfeeding increases the risk of iodine deficiency induced brain damage in the child and consequently an iodine supplement should be considered (22). Maternal smoking during pregnancy is a risk factor for ADHD (24). Smoking during pregnancy and breastfeeding should be widely discouraged.

5. A decreased consumption of bread (< 5 slices/day) (33.90%). In case of an increased consumption of bread (> 5 slices/day), we did not find a statistically significant difference between pregnant women with iodine supplements *versus* those without iodine supplements (Fig. 4); it must be added that the percentage of pregnant women with an intake of more than 5 slices of bread/day was 66.10 (around two-thirds) and this may contribute to the lack of difference between median UIC in endemic and nonendemic areas. On the other hand, in case of a lower bread consumption (< 5 slices/day) there is a statistically significant difference between pregnant women with iodine supplements (245.2 mcg/L) *vs.* those without iodine supplements (128.3 mcg/L) ($p = 0.027$) (Fig. 4). The last subgroup mentioned (less than 5 slices of bread/

day) associated with the lack of iodine supplements represents a vulnerability of the fetal brain to iodine deficiency, because median UIC was lower than 150 mcg/L. These data are comprehensible if we take into account that an additional increase of iodine intake is due to an excessive consumption of bread and other bakery products which is traditional in Romania and which often contains iodized salt after implementation of Universal Salt Iodization; in our country, bread is the staple food (5). According to some recent data from the Romanian National Institute of Statistics, the mean amount of bakery products consumed per day in Romania is 546 grams, in contrast with around 300 grams in the great majority of European countries (5).

The above mentioned five vulnerabilities were recorded at least once in every pregnant woman from the study group, supporting ATA and ETA recommendations: 150 mcg iodine/day in all pregnant women during pregnancy and breastfeeding (14, 18).

We consider that there are at least two additional vulnerabilities regarding developing fetal brain during pregnancy (not evaluated in this study):

- since most women become aware they are pregnant towards the end of the first trimester, iodine supplementation often does not cover the first trimester, when the developing fetal brain is especially vulnerable (2);

- the possible impact of pesticides as thyroid disruptors (mainly in the first trimester, probably being facilitated in the absence of iodine supplements) (25). Benefits of correcting iodine deficiency far outweigh its risks (26). Discrepancies between iodine status in schoolchildren and pregnant women may occur (27). Since in the iodine sufficient regions studied, the median UIC were normal also in women who did not receive iodine supplements during pregnancy, their use in these regions may be debated. However, some pregnant women from these areas may have other vulnerability factors mentioned above. Therefore we recommended iodine supplements during pregnancy even in these regions, since after supplementation the median UIC do not exceed the normal values for pregnancy.

In conclusion, median UIC in pregnant women was 206 mcg/L, reflecting iodine sufficiency during pregnancy. Moreover, the difference between the subgroup with iodine supplements (213.5 mcg/L) and the subgroup without iodine supplements (205.7 mcg/L) was not statistically significant, probably due to the excessive consumption of bread and other bakery products which is traditional in Romania and often

contain iodized salt after implementation of Universal Salt Iodization in our country, in January 2003. The results of this pilot study should be confirmed through extended nationwide, population-based, cross-sectional surveys.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgement

We would like to express our gratitude to Professor Anca Ioana for her kind help and precious guidance.

References

1. Pearce EN. Iodine deficiency in pregnant women in the UK: the costs of inaction. *Lancet Diabetes Endocrinol* 2015;3(9):671-672.
2. Zimmermann MB, Gizak M, Abbott K, Andersson M, Lazarus JH. Iodine deficiency in pregnant women in Europe. *Lancet Diabetes Endocrinol* 2015;3(9):672-674.
3. Obregon MJ, Escobar del RF, Morreale de EG. The effects of iodine deficiency on thyroid hormone deiodination. *Thyroid* 2005;15(8):917-929.
4. Lazarus JH. Iodine status in Europe in 2014. *Eur Thyroid J* 2014;3(1):3-6.
5. Ursu HI, Podia-Igna C, Delia CE, Toma GM, Goran D, Galoiu S, Niculescu DA, Giurgiu D, Gheorghiu ML, Anca IA. Iodine status after a decade of Universal Salt Iodization in Romania: a bicentric study in urban areas. *Acta Endo (Buc)* 2014;10(1):9-20.
6. Simescu M, Dumitriu L, Sava M, Cioverna D, Colda A, Balmes E, Ursu H, Bistriceanu M, Zosin I, Duncea I, Balasz J, Kun I, Dragatoiu G, Hazi G, Coamesu I, Harsan T, Stamoran L, Florescu E, Vitiuc M, Varcui M, Budura I, Fugaciu A, Hutanu T, Lepadatu D, Sulac H, Sirbu A. Urinary iodine levels in schoolchildren and pregnant women after the legislative changes in the salt iodization. *Acta Endo (Buc)* 2006;2(1):33-44.
7. Zimmermann MB. Iodine deficiency. *Endocr Rev* 2009;30(4):376-408.
8. Varlas V, Gheorghiu M. Fetal thyroid status in normal pregnancy and premature birth in euthyroid women without goitre from areas with or without iodine deficiency. *Acta Endo (Buc)* 2006;2(4):403-418.
9. Ursu HI, Ioachim D, Munteanu L. About the guideline for diagnosis and treatment of primary hyperparathyroidism in a country with endemic goiter. *Acta Endo (Buc)* 2010;6(1):129-138.
10. Ursu HI. The impact of iodine deficiency on perinatal morbidity and mortality. *Acta Endo (Buc)* 2012;8(4):619-625.
11. Toma A, Sava M, Delia C, Tomescu E, Simescu M, Coculescu M. Universal salt iodization effects on endemic goiter in Arges county, Romania. *Acta Endo (Buc)* 2005;1(2):167-180.
12. Toma A, Diaconu B, Gheorghiu M, Sava N, Nedelcu L, Trifanescu R, Sava M, Barbos D, Coculescu M. Persistence of neurological cretinism in old endemic goiter area of the Carpathians. *Acta Endo (Buc)* 2005;1(3):311-324.
13. Vanderpump MP, Lazarus JH, Smyth PP, Laurberg P, Holder RL, Boelaert K, Franklyn JA; British Thyroid Association UK Iodine Survey Group. Iodine status of UK schoolgirls: a cross-sectional survey. *Lancet* 2011;377(9782):2007-2012.
14. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy and in Children. *European Thyroid Journal*. 2014;3(2):76-94.

15. Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisa A, Artemisia A, Trimarchi F. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. *J Clin Endocrinol Metab* 2004; 89(12):6054-6060.
16. Hetzel BS. Iodine and neuropsychological development. *J Nutr* 2000;130(2S Suppl):493S-495S.
17. Moleti M, Trimarchi F, Tortorella G, Candia Longo A, Giorgianni G, Sturniolo G, Alibrandi A, Vermiglio F. Effects of maternal iodine nutrition and thyroid status on cognitive development in offspring: A pilot study. *Thyroid*. 2016;26(2):296-305.
18. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W; American Thyroid Association Taskforce on Thyroid Disease During Pregnancy and Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011;21(10):1081-1125.
19. Lozoff B, Georgieff MK. Iron deficiency and brain development. *Semin Pediatr Neurol* 2006;13(3):158-165.
20. Schmidt RJ, Tancredi DJ, Krakowiak P, Hansen RL, Ozonoff S. Maternal intake of supplemental iron and risk of autism spectrum disorder. *Am J Epidemiol* 2014;180(9):890-900.
21. Hess SY, Zimmermann MB, Adou P, Torresani T, Hurrell RF. Treatment of iron deficiency in goitrous children improves the efficacy of iodized salt in Cote d'Ivoire. *Am J Clin Nutr* 2002;75(4):743-748.
22. Laurberg P, Nohr SB, Pedersen KM, Fuglsang E. Iodine nutrition in breast-fed infants is impaired by maternal smoking. *J Clin Endocrinol Metab* 2004;89(1):181-187.
23. Andersen SL, Nohr SB, Wu CS, Olsen J, Pedersen KM, Laurberg P. Thyroglobulin in smoking mothers and their newborns at delivery suggests autoregulation of placental iodide transport overcoming thiocyanate inhibition. *Eur J Endocrinol* 2013;168(5):723-731.
24. Milberger S, Biederman J, Faraone SV, Chen L, Jones J. Is maternal smoking during pregnancy a risk factor for attention deficit hyperactivity disorder in children? *Am J Psychiatry* 1996;153(9):1138-1142.
25. Sullivan KM. The interaction of agricultural pesticides and marginal iodine nutrition status as a cause of autism spectrum disorders. *Environ Health Perspect* 2008;116(4):A155.
26. Braverman LE. Adequate iodine intake-the good far outweighs the bad. *Eur J Endocrinol* 1998;139(1):14-15.
27. Pearce EN, Andersson M, Zimmermann MB. Global iodine nutrition: Where do we stand in 2013? *Thyroid* 2013;23(5):523-528.