

# Iodine Deficiency, Still a Global Problem?

BIANCA GEORGIANA BIBAN<sup>1</sup>, CORINA LICHIARDOPOL<sup>2</sup>

<sup>1</sup>University of Medicine and Pharmacy of Craiova

<sup>2</sup>Department of Endocrinology, University of Medicine and Pharmacy of Craiova

**ABSTRACT:** Iodine Deficiency Disorders are a major public health problem worldwide affecting all groups of people of which children and lactating women are the most vulnerable categories. At a global scale, approximately 2 billion people suffer of iodine deficiency (ID) of which approximately 50 million present with clinical manifestations. Assessing iodine levels through different methods has proven to have a key role when discussing treatment options. Screening programs, and early ID diagnostic is important for pregnant women's follow-up, especially in known countries with iodine deficiency. Universal salt iodization programs have been proposed over the world, but unfortunately have covered about 71% of the world's population. The aim of this article is to address the current standings of iodine status and influence on general population with a general focus on newborns and pregnant women and to review the worldwide perspective on available prevention methods.

**KEYWORDS:** iodine deficiency, pregnancy, new-borns

## Introduction

ID is considered a major public health problem worldwide affecting all groups of people of which children and lactating women are the most vulnerable categories. At a global scale, approximately 2 billion people suffer of ID of which approximately 50 million present with clinical manifestations [1]. ID in daily food intake may result in an inadequate secretion of thyroid hormones, with major clinical consequences, especially neurological findings [2]. Although it may affect any age, ID consequences may appear from the foetus stage, due to an insufficient iodine food intake in the mother's diet. Thus, the most vulnerable age period is no doubt the womb as well as the natal stage, when differentiation, growth and brain development may be influenced by the inadequate quantities of Iodine and by the thyroid hormones with general consequences related to irreversible neurological disorders and mental retardation [3,4].

Assessing iodine levels through different methods has proven to have a key role when discussing treatment options. Screening programs, and early ID diagnostic is important for pregnant women's follow-up, especially in known countries with iodine deficiency. Universal salt iodization programs have been proposed over the world, even though have successfully covered only 71% of the population [5,6].

The aim of this article is to address the current standings of iodine status and influence on general population with a general focus on newborns and pregnant women and to review

the worldwide perspective on available prevention methods.

## What is Iodine Deficiency and what is its influence in pregnant women and newborns?

According to World Health Organization (WHO), the International Council for Control of Iodine Deficiency Disorders (ICCIDD) and the United Nations Children's Fund (UNICEF), a median urinary iodine concentration (UIC) below 100µg/l for nonpregnant woman and children defines an iodine deficient population, while the normal values for pregnant women should be between 150-249µg/l [7]. To put it in other words, both pregnant and lactating women have increased needs of iodine and therefore, numerous studies were conducted to see in which way the metabolism of the iodine is altered during pregnancy.

First of all, the renal loss of iodine is more significant in pregnant women presumably because of the fact that pregnancy is associated with an increase in renal function which is suggested by the mid-pregnancy 75% high renal plasma flow and from the late first trimester 50% higher glomerular filtration rate until the woman gives birth [8].

Changes occur in the thyroid gland as well, including a 50 % higher thyroid absolute iodine uptake (AIU), which is related to almost 50% increase of hormone production in the first pregnancy trimester [9]. Even from the early beginning of a pregnancy, human chorionic gonadotropin (hCG) can be detected at higher levels than usual. When hCG level raises it stimulates the thyroid gland to produce more thyroid hormones (thyroxine-T4 and

triiodothyronine-T<sub>3</sub>). In addition, another effect of hCG is to reduce the activity of iodothyronine deiodinase type 3 in the utero-placenta unit, an enzyme whose role is to inactivate T<sub>4</sub> and T<sub>3</sub> [10,11]. Due to these facts, in early pregnancy, serum thyroid-stimulating hormone (TSH) has decreased levels, thus, a shift in the balance between serum rT<sub>3</sub> and T<sub>3</sub>, in maternal circulation, may be noted.

To sum up, iodine levels during pregnancy may be caused by increased renal iodide clearance and increased thyroid hormone production to which we can add other factors such as the iodide transferred across the placenta to the fetus and a gradual 50% increase in protein-bound T<sub>4</sub> and T<sub>3</sub>.

### **When and how ID affects the development of the newborn?**

Pregnancy requires higher amounts of micronutrients and macronutrients than usual in order to maintain the health of both, mother and growing foetus. One of the most widespread micronutrient deficiencies worldwide is that of iodine. Iodine is a particularly important microelement in human physiology, required for normal physical growth during gestation and early life, and it is an essential component of the hormones produced by the thyroid gland whose absence or inadequate level can cause significant clinical manifestations such as increased risk of stillbirths, abortions, perinatal mortality, congenital abnormalities, cretinism, impaired growth [12-17].

Iodine deficiency disorders (IDD) generally refers to all the iodine deficiency effects in a population which may be prevented with a proper intake [18].

Brain development is a complex process that begins from early pregnancy and goes on for the first years of the newborn's life. This is the reason why ID's most serious consequences are the neurological ones [19,20]. Thyroid hormones are essential for a normal neurological development, being involved in myelination, cell differentiation and migration, growth, metabolism, sexual development, body temperature [21].

During pregnancy and lactation, two periods of increased demands, the fetus and infants are not capable to produce their own thyroid hormones. Thus, an important contribution is brought by the placenta which provides a connection between maternal and fetal circulation and after birth an adequate iodine concentration in breastmilk (BMIC) is essential [22]. According to Vulmsa *et al.* measurable T<sub>4</sub>

in cord serum was found in newborns who were not supposed to be able to synthesize thyroid hormones [23].

Many studies have correlated the the degree of ID with the thyroid functionality. The results showed that thyroid dysfunction may start to develop in pregnancy when urinary iodine excretion drops around 50µg/l.

It is well known that children born from mothers with severe ID during pregnancy have serious neurological disorders such as cretinism and mental retardation. Even more, the newborn may be characterized by a short stature, deafness and spasticity, all these clinical aspects being illustrative for the neurological cretinism [24]. Furthermore, Bath *et al.* [25] studied the connections between maternal iodine status and child IQ at the age of 8 and the ability to read at the age of 9. Thus, studies revealed the fact that the smallest quartile for verbal IQ, reading accuracy, and reading comprehension was more common in children of mothers with iodine to creatinine ratio below 150µg/g. Lower school performances have also been linked to mild ID [26].

The main clinical sign of ID in affected population is endemic goiter (EG) which represents thyroid's manner to adapt to an inadequate intake of iodine. Hence, TRH will be stimulated, TSH will grow and the consequence of prolonged TRH is the development of goiter.

Even if goiter is considered the cardinal sign of ID, in children, the most serious consequences are observed in growth and development. Decrease in insulin-like growth factor 1 (IGF) and IGF binding protein 3 (IGFBP) concentrations are also often associated with ID [27,28].

Questions have been raised regarding the connection between autism spectrum disorder (ASD) and ID. Even though ASD is a pluriethiological pathology including environmental, genetic, social factors, some studies performed in Egypt showed that more than half of the children with ASD were iodine deficient and another study performed in US revealed that autistic children had 45% lower iodine content in their hair than healthy children [29,30]. Also another Polish study aimed to asses boys iodine status with severe autism compared to their healthy peers and also to analyze the link between urinary iodine, thyroid hormones, body mass index and ASD symptomatology. Although some symptoms are connected to ID in maturing boys further investigation is needed in order to see if the

iodine supplementation can reverse some clinical manifestations [31].

Moreover, the incidence of ID and its effects in children with a diagnosis of attention deficit/hyperactivity disorder (ADHD) was investigated. A study including 89 children diagnosed with ADHD of whom 71.9% had mild iodine deficiency showed there was no significant relationship between urinary iodine levels with Wechsler intelligence scale for Children (WISC-R). However, subtest scores and Conners' parent rating scales (CPRS) revealed an association between urinary iodine levels and hyperactivity section of Conners' teacher rating scales (CTRS) [32].

### Excessive iodine intake

ID interferes with the normal thyroid function, but an iodine excess that comes as a correction of a previous ID, as a higher intake than normal, can also affect the gland's proper function, leading to an autoimmune disease, goiter, hypothyroidism, iodine-induced thyrotoxicosis or thyroid cancer. Healthy adults can tolerate iodine levels of 600-1100µg iodine/day without facing any side effects, however the safer upper level of intake in children or adults suffering from autoimmune thyroid disease should be much lower. Hence, the recommended daily intake is 150µg/day [33]. As far as breastfeeding women are concerned, a threshold for iodine intake has not been considered even though there are studies describing high levels of iodine in the breast milk [34,35,36].

In areas where people are exposed to a high level of iodine for a long time, a higher prevalence of the thyroid enlargement and subclinical hypothyroidism has been noticed especially in coastal areas of Japan because of their daily intake of seaweeds or Eastern China, due to drinking water from shallow wells with a high content of iodine [37,38]. The pathogenic mechanisms which lead to a thyroid misfunction might be the iodine effect on the thyroid as well as reversible inhibition of thyroid function by excess iodine (the Wolff-Chaikoff effect).

There are studies showing that an excess of iodine is a risk factor for the development of thyroid autoimmunity not only for animal models, but also for human population because iodine can have a both direct (intracellular oxidative stress) and indirect (activation of proinflammatory phenomena that recruit immunocompetent cells) effect on thyrocytes. In fact, a study illustrated how the incidence of Hashimoto's thyroiditis increased after the

introduction of iodine prophylaxis [39]. The same result was noticed in Slovenia 10 years after they increased the potassium iodide per kg of salt from 10 to 25mg [40].

Jod-Basedow phenomenon is an iodine-induced thyrotoxicosis which appears when TSH-independent thyrocytes are stimulated by iodine. Among the susceptible patients are the ones with Graves- Basedow disease and also the ones with nodular goiter living in moderate to mild iodine-deficient areas, if the population is facing an increase in the iodine intake in a short period of time. A lot of cases of Jod-Basedow phenomenon appeared in Tasmania after the introduction of iodized bread and iodine enriched foods imported from Australia [41]. Similarly, in Austria, increasing the quantity of potassium iodide per kg of salt from 10 to 20mg was followed by a bigger number of cases of thyrotoxicosis [42]. However, introducing the prophylaxis with salt ionization should decrease the number of people with toxic nodular goitre and a decrease in the susceptible population for Jod-Basedow phenomenon should be expected.

Thyroid cancer incidence has increased dramatically worldwide in the last years and iodine supplementation is thought to have a potential contribution [43]. However, some studies pointed out that the iodine intake does not affect the overall incidence of thyroid cancer [44]. While in areas with severe ID the PTC/FTC ratio was 0.19-1.7, in areas with mild ID the PTC/FTC ratio was 1.6-3.7 and in places where the iodine intake was high the same ratio had values between 3.4-6.5 [45,46]. Thus, the histotype distribution of differentiated thyroid cancer seems to be more influenced by iodine supplementation rather than the incidence in a population.

### Methods of assessing iodine status

There are several methods iodine status assessment in pregnant women but among these methods the one that brings the most significant information is the median UIC in 'a representative sample' [18].

Urinary iodine excretion in nonpregnant adults and schoolchildren in a certain area may be used as an indicator of iodine status in pregnant women living in the same area, but the results are not conclusive because, even in an iodine insufficient area, once a woman becomes pregnant she can change her diet leading to a higher dietary iodine intake. Moreover, urinary iodine excretion represents an indicator which highlights the iodine intake for the last hours or

days. In order to diagnose ID for individuals more than one sample per 24 hours needs to be analyzed. As a consequence, to quantify urinary iodine excretion, 24-hour samples of urine have to be collected and analyzed [47].

Therefore, UIC is recommended by WHO, UNICEF, and ICCIDD to assess the iodine level. UIC is calculated per urine volume. One of the disadvantages is the fact that UIC varies with the fluid intake, this being the reason why the selection of a representative sample might be difficult. On the other hand, UIC has the advantage of being a low cost technique. The simplest way for both the doctor and the patient would be to collect a urine sample when a pregnant woman comes to the hospital for a routine control, but that sample might not be illustrative because of a diet change in diet that may have occurred on that specific day. However, when performing an abdominal ultrasound some clinicians recommend high fluid intake to pregnant women for a better image of the fetus, leading to a diluted urine sample with a lower iodine concentration. In order to avoid this situation a urine sample may be collected when the woman visits the hospital and at the same time she can be provided with a vial for urine sampling to use it on a typical day at home.

Currently, the iodine/creatinine ratio ( $\mu\text{g}$  iodine/gram creatinine) is being used to adjust the variation of the urinary volume. Once again an adjustment had to be made because creatinine varies with age and gender and in order to calculate the 24-hour urinary iodine excretion ( $\mu\text{g}$  iodine/24 hours) the iodine/creatinine ratio is multiplied by an estimated age- and gender specific 24-hour creatinine excretion iodine/creatinine ratio is multiplied by an estimated age and gender specific 24-hour creatinine excretion. Also UIC has a diurnal

variation and tends to be lowered by fasting [48].

Serum thyroid stimulating hormone may be used as an indicator of iodine nutrition but it is not a sensitive marker of ID for children and pregnant women. Even though, ID tends to lower T4 and increase serum thyroid stimulating hormone (TSH), there are studies which revealed the fact that TSH often remains in the normal range [49]. In contrast, TSH is a sensitive indicator of iodine status in newborns. In neonates the thyroid contains less iodine but its turnover is higher and thus TSH will continue to be stimulated when the supply of iodine is low because the turnover will remain increased. In populations with mild to moderate ID, TSH tends to be lowered with age due to thyroid autonomy [50].

Although serum thyroglobulin is a thyroid specific protein whose levels in serum represent a valid marker of ID in population studies [51,52], a high serum thyroglobulin concentration may also be present in various thyroid disorders as a result of physiological changes in Thyroid size can be an indicator of a pathology and also it can be used as a long-term indicator of iodine status. In the past clinical examination was the main option used to estimate the thyroid size, however in a mild iodine deficiency this technique proved to have poor sensitivity and specificity [54]. Nowadays thyroid ultra-sonography is preferable in order to evaluate the thyroid size in mild ID because is a non-invasive, safe and painless technique which offers information not only about the size of the gland but also to look for nodules, to see if a thyroid nodule has substantially grown over time, or to perform ultrasound-guided thyroid biopsy [55].

**Table 1. Available methods of assessing the iodine status at population level according to WHO/UNICEF/ICCIDD**

<b>Methods</b>	<b>Advantages</b>	<b>Disadvantages</b>
<b>Median urinary iodine concentration (<math>\mu\text{g/L}</math>)</b>	<ul style="list-style-type: none"> <li>➤ affordable</li> <li>➤ relatively easy to collect in most population groups</li> <li>➤ can be measured in spot urine specimens from a representative sample of the target group</li> <li>➤ can be used for all categories of people</li> </ul>	<ul style="list-style-type: none"> <li>➤ varies with the ingestion of fluids</li> <li>➤ important to avoid contamination</li> <li>➤ does not provide direct information on thyroid function, but a low value suggests a population is at higher risk of developing thyroid disorders</li> </ul>



		<ul style="list-style-type: none"> <li>➤ not valuable for individual assesment</li> <li>➤ evaluate the iodine intake for the last few days</li> <li>➤ a large number of samples need to be collected because of the great variability of biological products</li> <li>➤ requires laboratory equipment and trained technicians.</li> </ul>
<b>Thyroid stimulating hormone (mIU/L)</b>	<ul style="list-style-type: none"> <li>➤ sensitive indicator of iodine status in the newborn period</li> <li>➤ minimal costs if a congenital hypothyroidism screening program is already in place</li> <li>➤ simple technique</li> <li>➤ can be measured from a dried blood sample</li> <li>➤ blood spots can be collected and stored for weeks in dry rooms with low temperature</li> </ul>	<ul style="list-style-type: none"> <li>➤ not useful if iodine antiseptics used at birth</li> <li>➤ relatively insensitive indicator of iodine nutrition in school-aged children and adults.</li> <li>➤ requires a standardized, sensitive assay</li> <li>➤ relatively sophisticated equipment required to quantitatively measure TSH</li> <li>➤ should be taken by heel-prick at least 48 hours after delivery or from the cord right after birth in order to avoid physiological newborn surge</li> </ul>
<b>Serum or whole blood thyroglobulin (µg/L)</b>	<ul style="list-style-type: none"> <li>➤ simple technique</li> <li>➤ collection of samples is easy</li> <li>➤ samples can be stored in cold, dry rooms</li> <li>➤ international reference range available</li> <li>➤ well correlated with the severity of iodine deficiency as measured by UI.</li> <li>➤ Can be used to measure the improvement of thyroid function within several months after iodine repletion</li> <li>➤ more sensitive indicator of iodine repletion than TSH or T4.</li> </ul>	<ul style="list-style-type: none"> <li>➤ expensive immunoassay</li> <li>➤ standard reference material is available, but needs validation</li> </ul>
<b>T3/T4</b>	<ul style="list-style-type: none"> <li>➤ reflects the function of the thyroid</li> </ul>	<ul style="list-style-type: none"> <li>➤ poor indicators of iodine status</li> </ul>
<b>Goiter Physical examination</b>	<ul style="list-style-type: none"> <li>➤ simple and quick</li> <li>➤ requires no special equipment</li> </ul>	<ul style="list-style-type: none"> <li>➤ poor sensitivity and specificity</li> <li>➤ response to iodine intake appears after a long period of time</li> <li>➤ experienced examiner</li> </ul>
<b>Goiter ultrasound</b>	<ul style="list-style-type: none"> <li>➤ noninvasive, quick and safe</li> <li>➤ feasible even in remote areas using portable equipment</li> <li>➤ international reference values available</li> </ul>	<ul style="list-style-type: none"> <li>➤ requires experience and training</li> <li>➤ responds only slowly to changes in iodine intake</li> <li>➤ requires expensive equipment</li> </ul>

## Salt ionization

Prophylactic measures for IDD are no doubt necessary. Salt iodization, the use of iodised oil or the fortification of milk, bread and water, should be taken into consideration. With all the efforts considered, nowadays there are still some ID areas and billions of people are confronting this condition. Despite the fact that salt ionization is an easy and affordable method to avoid the consequences of ID, there are plenty of European countries who did not develop prevention programs, which led to the persistency of a mild to moderate iodine shortage [56]. Even in countries where endemic cretinism or endemic goiter disappeared, prophylactic measures have to be continued and sustained indefinitely since ID may reappear in time. What makes a difference between the ID and other nutrients deficits is the fact that iodine status is linked more to geography rather than socio-economic development since the soil is deficient in iodine in large geographic areas, worldwide. [57-59].

Universal salt iodization is the first-line strategy which has been accepted as a safe and cost-effective measure to ensure sufficient iodine intake by all individuals [60]. In contrast, it is important to keep in mind that high levels of salt represents a risk factor cardiovascular diseases. Hence, one of the main recommendations for lifestyle modification in patients with cardiovascular diseases is to reduce the dietary amount of sodium [61,62]. In patients having ID, a restrictive diet with a salt intake below 5g/day will lead to more severe effects of the ID [63]. For example, in Poland, there is a great variety of products that represent a source of iodine such as water containing iodine naturally or enriched with iodine in the production process or meat and milk which comes from animals whose food has been enriched with iodine. Also, pharmaceutical products containing iodine come in handy when salt ionization is not enough. Consequently, when salt iodization fails and the iodine intake is still low, daily iodine supplementation is recommended especially to pregnant women, lactating women and infants [64,65]. As we mentioned before, pregnant women have a higher risk of ID due to the 50% increased requirements for maintaining normal maternal thyroid hormone levels [55].

However, the problem that is still debatable is what to do when the median exceeds  $UIC \geq 100 \mu\text{g/l}$ , but is lower than the  $150 \mu\text{g/l}$  recommended in pregnancy in an iodine

sufficient area. Should all pregnant woman take iodine supplements or the median UIC should be increased to  $150 \mu\text{g/l}$  by the mean of salt iodization? There are different points of view regarding this matter and the discordance in guidance from different authorities reflects the lack of information about the proper dosage of iodine that should be recommended in pregnancy. WHO/UNICEF/ICCIDD reached a consensus regarding this dilemma which says that a pregnant woman who lives in a country with a median  $UIC \geq 100 \mu\text{g/l}$  more than 2 years should not be advised to take iodine supplements [66]. On the other hand, the American Thyroid Association considers that iodine-containing supplements should be taken by all pregnant women, disregarding the iodine status in the area they come from [67]. Another approach of this problem has been stated by The European Thyroid Association who considers that the ideal solution is to create intrathyroidal stores of iodine by giving euthyroid to pregnant and lactating women containing  $150 \mu\text{g}$  iodine/day even before conception [68].

The opposing points of view led to other inquiries. Thus, it is important to determine which degree of iodine deficit during pregnancy is associated with brain damage. Analyzing the existing data stressed that, where endemic cretinism was frequently diagnosed, UIC was below  $20 \mu\text{g/day}$  [69,70]. Of great importance is the fact that a lower degree of ID often leads to other neurological impairments and abnormal behaviour [70,71]. While values of  $UIC < 50 \mu\text{g/day}$  are associated with a certain degree of brain issues, it seems that mild ID ( $UIC$  in the range of  $50-99 \mu\text{g/day}$ ) is not harmful for the newborn. There is no convincing evidence that pregnant women with UIC below  $100 \mu\text{g/day}$  who took iodine supplements had a better outcome of pregnancy [70,72].

## Conclusion

Iodine represents a critical agent in the thyroid function. Iodine deficiency should focus more on prevention and early diagnosis, as future supplementation of iodine after a certain age surely does not reverse neurological disorders or reduce the size of large nodular goiters. Future complications may be prevented through different testing methods which are capable of easily identifying iodine deficiency, starting from alimentary questionnaires to urine tests as well as the thyroid hormones level.

## Acknowledgements

Biban B.G. and Lichiardopol C performed the literature search and wrote the paper.

## References

- Lazarus JH: The importance of iodine in public health. *Environ Geochem Health* 2015; 37: 605-618.
- Fiore E, Tonacchera M, Vitti P. Influence of iodization programmes on the epidemiology of nodular goitre. *Best Pract Res Clin Endocrinol Metab.* 2014; 28:577-88
- Sun X, Shan Z, Teng W. Effects of increased iodine intake on thyroid disorders. *Endocrinol Metab (Seoul).* 2014; 29:240-7.
- Andersen SL: Iodine status in pregnant and breastfeeding women: a Danish regional investigation. *Dan Med J* 2015; 62:B5074.
- Zimmermann MB, Gizak M, Abbott K, Andersson M, Lazarus JH: Iodine deficiency in pregnant women in Europe. *Lancet Diabetes Endocrinol* 2015; 3: 672-674.
- Andersen SL<sup>1</sup>, Laurberg P<sup>2</sup>. Iodine Supplementation in Pregnancy and the Dilemma of Ambiguous Recommendations *Eur Thyroid J.* 2016 Mar;5(1):35-43
- Iodine status worldwide: WHO global database on iodine deficiency. Geneva: World Health Organization
- Mortimer RH, Galligan JP, Cannell GR, Addison RS, Roberts MS: Maternal to fetal thyroxine transmission in the human term placenta is limited by inner ring deiodination. *J Clin Endocrinol Metab* 1996; 81: 2247-2249.
- Burrow GN, Fisher DA, Larsen PR: Maternal and fetal thyroid function. *N Engl J Med* 1994; 331: 1072-1078.
- Roti E, Fang SL, Green K, Emerson CH, Braverman LE: Human placenta is an active site of thyroxine and 3,3',5'-triiodothyronine tyrosyl ring deiodination. *J Clin Endocrinol Metab* 1981; 53: 498-501.
- Chan S, Kachilele S, Hobbs E, Bulmer JN, Boelaert K, McCabe CJ, Driver PM, Bradwell AR, Kester M, Visser TJ, Franklyn JA, Kilby MD: Placental iodothyronine deiodinase expression in normal and growth-restricted human pregnancies. *J Clin Endocrinol Metab* 2003; 88: 4488-4495.
- J.H. Lazarus, Iodine status in Europe in 2014, *Eur. Thyroid J.* (3) (2014) 3-6.
- F. Ahad, S.A. Ganie, Iodine, Iodine metabolism and Iodine deficiency disorders revisited, *Indian J. Endocrinol. Metab.* 14 (1) (2010) 13-17.
- B.S. Hetzel, Iodine and neuropsychological development, *J. Nutr.* 130 (2SSuppl) (2000) 493S-495S.
- M.B. Zimmermann, Iodine requirements and the risks and benefits of correcting iodine deficiency in populations. Review, *J. Trace Elem. Med. Biol.* 22 (2008) 81-92.
- M.B. Zimmermann, Iodine deficiency disorders and their correction using iodized salt and /or iodine supplements, in: T. Kaiho (Ed.), *Iodine Chemistry and Applications*, Wiley, 2015, 2015, pp. 421-431.
- C. Trumpff, S. De, J. chepper, J. Tafforeau, O. Van, H. yen, J. Vanderfaillie, Vandevijvere S, Mild iodine deficiency in pregnancy in Europe and its consequences for cognitive and psychomotor development of children: A review, *J. Trace Elem. Med. Biol.* 27 (2013) 174-183.
- WHO, UNICEF, ICCIDD. Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers. World Health Organisation 2007;3:1-98.
- Delange F. The role of iodine in brain development. *Proc Nutr Soc* 2000;59:75-79.
- Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Is neuropsychological development related to maternal hypo-thyroidism or to maternal hypothyroxinemia? *J Clin Endocrinol Metab* 2000;85:3975-3987.
- Bernal J. Thyroid hormones and brain development. *Vitam Horm* 2005;71:95-122.
- Azizi, F.; Smyth, P. Breastfeeding and maternal and infant iodine nutrition. *Clin. Endocrinol.* 2009, 70, 803-809.
- Vulsma T, Gons MH, de Vijlder JJ. Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. *N Engl J Med* 1989; 321:13-16.
- Eastman CJ, Zimmermann M. The Iodine Deficiency Disorders. [Updated 2014 Feb 12]. In: De Groot LJ, Chrousos G, Dungan K, et al., editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK285556/>
- Bath SC1, Steer CD, Golding J et al. 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* 2013; 382: 331-337
- Hynes KL, Otahal P, Hay I, et al. (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.
- Zimmermann MB, Jooste PL, Mabapa NS, Mbhenyane X, Schoeman S, Biebinger R, Chaouki N, Bozo M, Grimci L, Bridson J. Treatment of iodine deficiency in school-age children increases insulin-like growth factor (IGF)-I and IGF binding protein-3 concentrations and improves somatic growth. *J Clin Endocrinol Metab* 2007;92:437-42.
- Koutras DA, Christakis G, Trichopoulos D, Dakou-Voutetaki A, Kyriakopoulos V, Fontanares P, Livadas DP, Gatsios D, Malamos B. Endemic goiter in Greece: nutritional status, growth, and skeletal development of goitrous and non goitrous populations. *Am J Clin Nutr* 1973;26:1360-8.
- R.T. Hamza, D.H. Hewedi, M.T. Sallam, Iodine deficiency in Egyptian autistic children and their mothers: relation to disease severity, *Arch. Med. Res.* 44 (7)(2013) 555-561.
- J.B. Adams, C.E. Holloway, F. George, D. Quig, Analyses of toxic metals and essential minerals in the hair of Arizona children with autism and associated conditions, and their mothers, *Biol. Trace Elem. Res.* 110 (3) (2006) 193-210.

31. Anna Bla`zewicz, Agata Makarewicz, Izabela Korona-Glowniak, Wojciech Dolliver, Ryszard Kocjan, Iodine in autism spectrum disorders, *Journal of Trace Elements in Medicine and Biology* 34 (2016) 32-37
32. Saliha Kanik Yuksek, Zehra Aycan, Ozgur Oner, Evaluation of Iodine Deficiency in Children with Attention Deficit/Hyperactivity Disorder, *J Clin Res Pediatr Endocrinol* 2016;8(1):61-66
33. Roti, E., and Vagenakis, A.G. 2000. Effect of excess iodide: clinical aspects. In *The thyroid. A clinical and fundamental text*. L.E. Braverman, and R.D. Utiger, editors. Philadelphia: J.B. Lippincott, Williams and Wilkins publ. 316-329.
34. WHO. Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers. 2nd ed. World Health Organisation, International Council for Control of Iodine Deficiency Disorders, United Nations Children's Fund; 2007.
35. Rhee SS, Braverman LE, Pino S, He X, Pearce EN. High iodine content of Korean seaweed soup: a health risk for lactating women and their infants. *Thyroid* 2011;21:927-8.
36. Chung HR, Shin CH, Yang SW, Choi CW, Kim BI. Subclinical hypothyroidism in Korean preterm infants associated with high levels of iodine in breast milk. *J Clin Endocrinol Metab* 2009;94:4444-7.
37. Ma, T., Zhi-Heng, Y., Ti-Zhang, L., Shi-Ying, W., Cheng-Fang, D., Xuan-Yang, H., Hui-Cheng, Z., Rong-Ning, L., Chen-Yun, Y., Guo-Qiang, W., et al. 1982. High-iodide endemic goiter. *Chin. Med. J.* 95:692-696.
38. Zhao, J., Wang, P., Shang, L., Sullivan, K.M., Haar, F.v.d., and Maberly, G. 2000. Endemic goiter associated with high iodine intake. *Amer. J. Publ. Hlth* 90:1633-1635.
39. Lombardi F. A., Fiore E., Tonacchera M., et al. The effect of voluntary iodine prophylaxis in a small rural community: the pescopagano survey 15 years later. *The Journal of Clinical Endocrinology & Metabolism*. 2013;98(3):1031-1039.
40. Zaletel K., Gaberscek S., Pirnat E. Ten-year follow-up of thyroid epidemiology in Slovenia after increase in salt iodization. *Croatian Medical Journal*. 2011;52(5):615-621.
41. Vidor G. I., Stewart J. C., Wall J. R., Wangel A., Hetzel B. S. Pathogenesis of iodine-induced thyrotoxicosis: studies in Northern Tasmania. *The Journal of Clinical Endocrinology & Metabolism*. 1973;37(6):901-909.
42. Mostbeck A., Galvan G., Bauer P., et al. The incidence of hyperthyroidism in Austria from 1987 to 1995 before and after an increase in salt iodization in 1990. *European Journal of Nuclear Medicine*. 1998;25(4):367-374.
43. Blomberg M., Feldt-Rasmussen U., Andersen K. K., Kjaer S. K. Thyroid cancer in Denmark 1943-2008, before and after iodine supplementation. *International Journal of Cancer*. 2012;131(10):2360-2366.
44. Feldt-Rasmussen U. Iodine and cancer. *Thyroid*. 2001; 11(5):483-486.
45. Dijkstra B., Prichard R. S., Lee A., et al. Changing patterns of thyroid carcinoma. *Irish Journal of Medical Science*. 2007;176(2):87-90.
46. Harach H. R., Escalante D. A., Onativia A., Lederer Outes J., Saravia Day E., Williams E. D. Thyroid carcinoma and thyroiditis in an endemic goitre region before and after iodine prophylaxis. *Acta Endocrinologica*. 1985;108(1):55-60.
47. Vejbjerg P, Knudsen N, Perrild H, Laurberg P, Andersen S, Rasmussen LB, et al. Estimation of iodine intake from various urinary iodine measurements in population studies. *Thyroid* 2009;19:1281-1286.
48. Rasmussen LB, Ovesen L, Christiansen E. Day-to-day and within-day variation in urinary iodine excretion. *Eur J Clin Nutr* 1999;53:401-407.
49. Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Role of thyroid hormone during early brain development. *Eur J Endocrinol* 2004;151:U25-U37.
50. Laurberg P, Andersen S, Bjarnadottir RI, Carle A, Hreidarsson A, Knudsen N, et al. Evaluating iodine deficiency in pregnant women and young infants-complex physiology with a risk of misinterpretation. *Public Health Nutr* 2007;10:1547-1552.
51. Knudsen N, Bulow I, Jorgensen T, Perrild H, Ovesen L, Laurberg P. Serum Tg-a sensitive marker of thyroid abnormalities and iodine deficiency in epidemiological studies. *J Clin Endocrinol Metab* 2001;86:3599-3603.
52. Vejbjerg P, Knudsen N, Perrild H, Laurberg P, Carle A, Peder-sen IB, et al. Thyroglobulin as a marker of iodine nutrition status in the general population. *Eur J Endocrinol* 2009;161:475-481.
53. Laurberg P, Andersen S, Bjarnadottir RI, Carle A, Hreidarsson A, Knudsen N, et al. Evaluating iodine deficiency in pregnant women and young infants-complex physiology with a risk of misinterpretation. *Public Health Nutr* 2007;10:1547-1552.
54. Zimmermann MB, Hess SY, Molinari L, et al. New reference values for thyroid volume by ultrasound in iodine-sufficient schoolchildren: a WHO/NHD Iodine Deficiency Study Group Report. *Am J Clin Nutr* 2004; 79: 231-37.
55. Zimmermann MB. Iodine deficiency. *Endocr Rev* 2009;30:376-408.
56. Podoba J, Racova K, Urbankova H, Srbecky M. Current status of iodine deficiency-related disorders prophylaxis in Slovakia - the life's work of Julian Podoba remained unfinished. *ENDOCRINE REGULATIONS*, Vol. 50, 3-9, 2016
57. Zimmermann MB. Symposium on 'Geographical and geological influences on nutrition': iodine deficiency in industrialised countries. *Proc Nutr Soc* 2010;69:133-43.
58. Eastman CJ, Zimmermann MB. The iodine deficiency disorders. In: *Thyroid disease manager*. 2009
59. World Health Organization; United Nations Children's Fund, International Council for Control of Iodine Deficiency Disorders. Progress towards the elimination of iodine deficiency disorders (IDD). Geneva (Switzerland): WHO; 1999.



60. World Health Organization, United Nations Children's Fund, International Council for the Control of Iodine Deficiency Disorders. Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers. 3rd edn Geneva, Switzerland: World Health Organization, 2007.
61. WHO Forum and Technical Meeting on Reducing Salt Intake in the Population. Paris, France. October. WHO, 2006.
62. WHO, Report of a WHO Expert Consultation Salt as a Vehicle for Fortification, Luxembourg 21-22 March. WHO, 2007.
63. Algorithm of conduct in arterial hypertension-year 2011. Guidelines of the Polish Society of Hypertension. Arterial Hypertension 2011; 15: 55-82.
64. Szybiński Z. Iodine deficiency in pregnancy-a continuing public health problem. Endokrynol Pol 2005; 56: 65-71.
65. Glinoer D. The regulation of thyroid function during normal pregnancy: importance of the iodine nutrition status. Best Pract Res Clin Endocrinol Metab 2004; 18: 133-152.
66. WHO Secretariat, Andersson M, de Benoist B, Delange F, Zupan J; Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. Public Health Nutr. 2007 Dec; 10(12A):1606-11.
67. Public Health Committee of the American Thyroid Association, Becker DV, Braverman LE, Delange F, Dunn JT, Franklyn JA, Hollowell JG, Lamm SH, Mitchell ML, Pearce E, Robbins J, Rovet JF Iodine supplementation for pregnancy and lactation-United States and Canada: recommendations of the American Thyroid Association. Thyroid. 2006 Oct; 16(10):949-51.
68. Hubalewska-Dydejczyk A, Lewiński A, Milewicz A et al. Management of thyroid diseases during pregnancy. Endokrynol Pol 2011; 62: 362-381
69. Pharoah PO, Buttfield IH, Hetzel BS: Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. Lancet 1971; 1: 308-310.
70. Stine Linding Andersen, Peter Laurberg Iodine Supplementation in Pregnancy and the Dilemma of Ambiguous Recommendations, Eur Thyroid J 2016;5:35-43 DOI: 10.1159/000444254
71. Lancet 2013; 382: 331-337. 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: 6054-6060.
72. Glinoer D, De Nayer P, Delange F, Lemone M, Toppet V, Spehl M, Grun JP, Kinthaert J, Lejeune B: A randomized trial for the treatment of mild iodine deficiency during pregnancy: maternal and neonatal effects. J Clin Endocrinol Metab 1995; 80: 258-269.

---

*Corresponding Author: Bianca Georgiana Biban, University of Medicine and Pharmacy of Craiova, 2 Petru Rareș Street, 200349 Craiova, Dolj County, Romania; e-mail: bianca.biban.g@gmail.com*