



SPECIAL ARTICLE

Iodine supplementation during pregnancy and lactation. Position statement of the Working Group on Disorders Related to Iodine Deficiency and Thyroid Dysfunction of the Spanish Society of Endocrinology and Nutrition[☆]

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Abstract Severe iodine deficiency and mild iodine deficiency during pregnancy and lactation affect thyroid function of the mother and neonate as well as the infant's neuropsychological development. Studies performed in Spain confirm that most women are iodine deficient during pregnancy and lactation. Pregnant and breast feeding women and women planning to become pregnant should take iodine supplements.

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PALABRAS CLAVE

Deficiencia de yodo;
Suplementación de
yodo;
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Lactancia

Suplementación con yodo durante el embarazo y la lactancia. Toma de posición del Grupo de Trabajo de Trastornos relacionados con la Deficiencia de Yodo y Disfunción Tiroidea de la Sociedad Española de Endocrinología y Nutrición

Resumen La deficiencia de yodo grave y moderada durante el embarazo y la lactancia afecta a la función tiroidea de la madre y del neonato, así como al desarrollo neuropsicológico del niño. Estudios realizados en España confirman que la mayoría de las mujeres se encuentran en

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◇ The names of the members of the group Working Group related to Iodine Deficiency and Thyroid Dysfunction of the Spanish Society of Endocrinology and Nutrition are listed in Annex 1 to the end of Article Disorders.

iododeficiencia durante la gestación y la lactancia. Las mujeres embarazadas, las que amamantan a sus hijos y las que planifican su gestación deberían recibir suplementos de yodo.
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Introduction

On October 30, 2012, a workshop on "Iodine and folic acid supplementation during pregnancy and lactation" organized by the Directorate of Public Health of the Basque Government and the Directorate General of Research and Public Health of the Valencian Government was held in Bilbao, Spain. The final recommendations of this workshop (BW)¹ included the following conclusion, based on the statement that iodine contents of iodinated salt (IS), milk, and dairy products are sufficient to cover iodine requirements in pregnancy and lactation provided the mother takes these products adequately: "*Universal supplementation with (potassium iodide) tablets during pregnancy and breast-feeding is not currently justified in Spain*". Thus, according to the conclusions of the workshop, pharmacological iodine supplementation during pregnancy and lactation should be selective, and should only be prescribed to women at a high risk of inadequate iodine intake or the development of thyroid dysfunction at these stages.¹

Less than three weeks before the BW, the journal *ENDOCRINOLOGÍA Y NUTRICIÓN* had published an editorial signed by the Working Group on Disorders Related to Iodine Deficiency and Thyroid Dysfunction (IDD-TD) entitled "Eradication of iodine deficiency in Spain. Close but not there yet".² This article alerted its readers to the risk that the currently adequate iodine nutritional status in Spanish children and adults, mainly achieved through silent or uncontrolled iodine prophylaxis, could change and iodine deficiency (ID) could reappear, as has recently occurred in other European countries.³

Because of the almost simultaneous dissemination of two documents proposing conflicting strategies for ID correction, our Working Group on IDD-TD considered it indispensable to analyze the BW document, disseminated by electronic means, not published in any scientific journal, and which has not been explicitly endorsed either by the Working Group on IDD-TD as such, or by other scientific bodies (Spanish Society of Gynecology and Obstetrics, Spanish Society of Family and Community Medicine, Spanish Society of Rural and General Practitioners, Spanish Society of General Practitioners, Spanish Pediatrics Society) whose members are implicated in the management of iodine supplementation to pregnant or lactating women.

This article analyzes changes over time in the correction of gestational ID in Spain and reviews the evidence available on iodine supplementation in pregnant and lactating women, taking into account that iodine requirements in these two groups are almost double those of the remaining adult population.

Changes over time in iodine deficiency in Spain

After more than four decades of documented ID in Spain, in 2004 the World Health Organization (WHO) included Spain among the countries with optimum iodine nutrition.⁴ Several recent studies conducted in schoolchildren,⁵ adults,⁶ and pre-schoolchildren⁷ show median urinary iodine levels higher than 100 µg/L confirming iodine sufficiency in those groups of the Spanish population. However, as reported by some authors⁸ in similar circumstances to those found in Spain, pregnant women may still have ID. The recent study by Arrobas-Velilla et al.⁹ showing the persistence of ID in a pregnant population despite a prior iodine supplementation campaign confirmed the high risk of this deficiency in pregnant women.

Various studies conducted in Spain between 1995 and 2004¹⁰ showed that more than 50% of the pregnant population were at risk of ID. The Spanish Ministry of Health therefore approved from 2005 the marketing of potassium iodide supplements (IKS) for ID prophylaxis reimbursed by the National Health System.¹¹

Although the BW's conclusions insinuate that IKS are almost universally used by pregnant women in Spain,¹ the truth is that substantial differences exist between the different autonomous communities as regards both institutional iodine prophylaxis programs for pregnant women and adherence to IKS prescription.⁹ In any case, and despite the use of IKS since 2005, most studies conducted after this date show a persistence of ID (defining iodine sufficiency in pregnant population as median urinary iodine levels of 150–249 µg/L¹²) in a high proportion of pregnant Spanish women. Thus, median urinary iodine levels less than 150 µg/L are found in pregnant women in the Basque Country,¹³ Castile-Leon,^{14,15} Castile-La Mancha,¹⁶ Madrid,¹⁷ Extremadura,¹⁸ Catalonia,^{19,20} the Valencian Community,^{20–22} and Andalusia,^{9,23} showing the almost universal current prevalence of ID in pregnant Spanish women.

Standard iodine prophylaxis measures, which include promoting the consumption of seafood and iodine-enriched food items such as salt and dairy products, cannot guarantee an adequate iodine nutritional status in pregnant women.¹¹ In 2004, the Working Group on IDD-TD therefore advised that the diet of any pregnant and/or lactating woman be supplemented with at least 150 µg of iodine daily as IK,²⁴ a recommendation which has been confirmed in subsequent publications of group members or on behalf of the Group on IDD-TD.^{25–29}

Limitations of standard iodine prophylaxis for the correction of iodine deficiency during pregnancy and lactation

Pregnant women experience a number of physiological changes in iodine metabolism, including increased urinary iodine excretion, iodine transfer from maternal circulation to the fetoplacental unit, and increased iodine requirements of the fetal thyroid gland from the second half of pregnancy.³⁰ Daily iodine requirements also increase during lactation due to iodine concentration in breast milk.³¹

In the general population, the routine use of IS, either individually (if present in more than 90% of households) or through universal iodination (defined as the iodination of all salt intended for human and animal consumption, including salt used by the food industry), is the best way to guarantee adequate dietary iodine provision according to the recommendations of the WHO and other international organizations.³² The correction of ID through other dietary sources of iodine, such as milk and dairy products, has the disadvantage of the lack of control of the amount of iodine entering the food chain.³³ Experiences such as the one recently reported in the United Kingdom³ should alert us to the necessity of implementing epidemiological surveillance measures that promote the consolidation of current achievements to avoid ID recurrence.

Many studies conducted on the pregnant Spanish population before¹¹ and after^{28,34,35} IKS availability show that most pregnant women, including those taking IS, do not achieve the adequate iodine nutritional status required in pregnancy without IK supplementation. Finally, with the exception of the Tirokid study,⁵ showing IS consumption by almost 70% of schoolchildren aged 6–7 years, the most recent studies conducted in adults,⁶ pre-schoolchildren,⁷ and schoolchildren aged 6–14 years³⁶ showed IS consumption rates close to 50%, which are still far away from the proportion of 90% of households established by different international organizations as one of the iodine sufficiency criteria.³²

To sum up, analysis of the current situation in Spain shows that there is ID persistence in most pregnant women based on the criteria set out by international organizations,³² that IS consumption does not exceed 50% in most cases, and that an overall situation of ID is most likely corrected by the effect of silent or uncontrolled iodine prophylaxis through the consumption of dairy products² whose mid-term efficacy and sustainability have very recently been questioned in other European countries³ and previously denounced in Spain.³⁷

Evidence that these dietary iodine sources were insufficient to correct ID in pregnancy recently led to the addition of IKS to the diet in all pregnant and lactating women being recommended.^{25–29} The idea that those same dietary sources can now correct ID does not appear to be supported by the reality of the Spanish situation.

Thus, the assumption by the BW and the dissemination among healthcare professionals of the concept that iodine requirements during pregnancy and lactation may be met with iodine contents in IS, milk, and dairy products only, and its recommendation of selective IKS in pregnant and lactating women at high risk of iodine deficiency, could put the clock back and return us to those strategies for

gestational ID correction in Spain used for decades during the past century and so perpetuate ID in pregnant women. As noted by some authors,³⁸ pregnancy and lactation are periods during which adequate nutrition is exceptionally important “because the child is not protected from an inadequate diet of the mother”.

Benefits and risks of pharmacological iodine supplementation

In pregnant women, a lack of iodine in their diet leads to an ID status that subsequently affects the fetus. Under these circumstances, maternal hypothyroxinemia, negatively affecting fetal brain development and aggravated by fetal hypothyroidism, occurs.³⁹ Cretinism represents the most severe form of the broad spectrum of developmental changes of the central nervous system caused by maternal ID, with various grades of intellectual impairment depending on ID severity.⁴⁰ Many epidemiological studies have unequivocally shown that severe ID results in increased infertility and miscarriage rates, increased neonatal mortality and a prevalence of congenital malformations, and children with low birthweight, in addition to the abovementioned intellectual developmental changes.⁴⁰ Various intervention studies have shown the benefits of correcting severe ID, especially in neuropsychological developmental changes.⁴¹ Finally, two meta-analyses^{42,43} including different types of studies reached similar conclusions: severe ID, especially in children, reduces the intelligence quotient by a mean of 12–13.5 points as compared to children from an iodine-sufficient control population.

Over the past decades, various studies have shown that during pregnancy and lactation, not only severe, but also mild and moderate ID may cause significant maternal–fetal complications.⁴⁴ In pregnant women, moderate ID (defined as urinary iodine levels ranging from 50 to 150 µg/day) increases the risk of goiter development in both the mother and fetus.⁴⁵ In addition, decreases in maternal thyroid hormone levels associated with moderate ID may cause intellectual and neuropsychomotor deficiencies in the offspring.⁴⁶ Finally, an increased frequency of attention deficit and hyperactivity disorders has been reported in children born to mothers with moderate ID.⁴⁷

The effects of iodine supplementation in pregnant women from European regions with moderate ID have been assessed in different studies. Eight controlled studies are currently available.^{48–55} Iodine doses and the time of start of iodine supplementation were different in these studies, and only two of them assessed the effects on neuropsychological development of the offspring.^{49,55} In pregnant women with moderate ID, iodine supplementation decreased maternal and fetal thyroid volume and umbilical cord thyroglobulin levels. No significant differences were found between the groups in maternal or cord levels of total T₄ and T₃ and free T₄. The two studies including neuropsychological assessment^{49,55} found that iodine supplementation in early pregnancy improved neurocognitive development. The increased neonatal thyroid-stimulating hormone (TSH) levels in cord blood from women given iodine supplements seen in two of the studies^{52,55} would appear to suggest that in iodine-deficient areas, the fetal thyroid gland may be

particularly sensitive to the inhibitory effects of iodine. This has been interpreted by some authors as a potential harmful effect on the newborn of maternal iodine supplementation, but the effect does not appear to be so harmful considering that the best neurodevelopmental scores were found in these children,²⁶ particularly in those whose mothers were given supplement in early pregnancy.^{49,55} The time of start of iodine supplementation in pregnant women appears to be a critical factor for its benefits on the neurodevelopment of their offspring. The benefits are decreased if supplementation is started after weeks 10–20 of pregnancy.⁴⁹ Similarly, the benefits of iodine supplementation on maternal thyroid function appear to depend to a greater extent on the pregestational start of supplementation than on the doses or on the ways to increase iodine intake by pregnant women.³⁴

A recent systematic review of iodine supplementation during pregnancy⁵⁶ selected 40 studies whose grade of evidence was classified as convincing, probable, indicative, and inconclusive. The results showed the evidence as being indicative both of the improvement in iodine nutritional status and thyroid function by iodine supplementation during pregnancy, and of the relationship between improved thyroid function during pregnancy and cognitive function in the offspring until 18 months of age.

The potential risk of pharmacological iodine supplementation has been assessed by different authors. The possibility that this supplementation could increase the prevalence of postpartum thyroiditis (PPT) in areas with moderate ID has been ruled out in several controlled clinical trials showing that IKS does not increase the prevalence and severity of PPT or maternal thyroid autoimmunity.^{48,57} Finally, iodine supplementation after delivery is not associated with an increased prevalence of PPT either.⁵⁸

The above discussed increase in neonatal TSH levels in infants born to mothers given iodine supplementation seen in two of the controlled studies^{52,55} suggests that, in iodine-deficient areas, the fetal thyroid gland may be particularly sensitive to the inhibitory effects of iodine, but that this does not have an apparent impact on the subsequent development of these children.

Although one study⁵⁹ reported that a higher daily iodine intake is associated with an increased frequency of TSH levels $> 4 \mu\text{U}/\text{mL}$ in the first trimester of pregnancy, which is in turn associated with poorer results in neuropsychological tests conducted in children at the age of one year, there have been no subsequent controlled studies supporting these findings. A recent observational study by Moleti et al.⁶⁰ reported that the TSH elevation found in women given supplemental iodine preparations may be due to a transient phenomenon of thyroid gland stunning, and the authors not only do not advise against iodine supplementation, but actually recommend that supplementation be started several months before pregnancy in order to avoid a sharp increase in iodine provision during pregnancy. However, the Moleti et al. study demonstrated that the prevalence of low maternal T_4 levels, a determinant factor for poorer fetal cerebral development,³⁵ was similar in the group of pregnant women treated with IKS and in those who had only taken IS, and that the incidence of low T_4 levels was lower in both cases as compared to women receiving no iodine supplementation during pregnancy.

The changes in both maternal and neonatal TSH levels seen in some studies in pregnant women receiving iodine supplements in areas with moderate ID very probably represent the adaptation phenomena of the maternal and fetal thyroid glands to the increased iodine provision needed during pregnancy. To date, there has not been a clear demonstration that such adaptive phenomena are associated with increased maternal–fetal morbidity, whereas evidence exists of the harmful effects of maternal hypothyroxinemia on neuronal development, extremely common in women with uncorrected gestational ID.

Recommendations of professional bodies for the prevention and correction of iodine deficiency during pregnancy and lactation

Ideally, standard iodine prophylaxis measures such as routine IS consumption should ensure the adequate replenishment of thyroid iodine deposits before pregnancy. However, as previously discussed, the current situation in Spain and most other European countries is far from this ideal situation.²⁶ During the past decades, there has been a gradual decrease in dietary iodine intake in most Western countries related, among other factors, to the decreased iodine contents of dairy products, recommendations to decrease daily salt intake for high blood pressure control, and the use of non-iodinated salt in most products of the food industry.⁶¹ The recent reappearance of iodine deficiency in Australia, New Zealand, and the United Kingdom,⁶² as well as the gradual decrease in urinary iodine excretion in the adult population of the United States⁶³ are clear examples of the effects of this decreased dietary intake of iodine. These facts, added to successive changes in the iodine requirements estimated by the various scientific bodies and international organizations, have led to new recommendations for ID correction, especially in pregnant and lactating women.

In 2005, the WHO recommended a iodine intake of $200 \mu\text{g}/\text{day}$ for women during pregnancy and $250 \mu\text{g}/\text{day}$ during lactation⁶⁴; these levels were increased to $250 \mu\text{g}/\text{day}$ from 2007.¹² Since 2006, the United States Institute of Medicine recommends a iodine intake of $220 \mu\text{g}/\text{day}$ during pregnancy and $290 \mu\text{g}/\text{day}$ during lactation.⁶⁵ The maximum tolerated iodine level, defined as the maximum daily amount of iodine ingested probably having no risk of causing adverse effects on health in most people,⁶⁵ has been established at $1100 \mu\text{g}/\text{day}$ ⁶⁴ and at $600 \mu\text{g}/\text{day}$ in Europe.⁶⁶ These maximum levels do not apply to pregnant women who are receiving potassium iodide supplements and under medical monitoring.²⁵ Because of the progressive decrease in urinary iodine excretion seen in the US adult population⁶³ and the significance of ID during pregnancy,³⁹ the American Thyroid Association recommended in its 2011 guidelines⁶⁷ that all US women who are pregnant, breast-feeding, or planning pregnancy take daily dietary supplements providing $150 \mu\text{g}/\text{day}$ of iodine. More recently, the Endocrine Society⁶⁸ recommended that prenatal multivitamin preparations include $100\text{--}200 \mu\text{g}$ of iodine per dose. As noted by several authors, the addition of $150 \mu\text{g}$ of iodine involves no risk even in women with an adequate replenishment of thyroid iodine deposits,

because iodine intakes as high as 500 or 1100 µg daily, the maximum tolerated iodine levels, are considered safe during pregnancy⁶⁹ and, on the other hand, iodine doses recommended in prevention programs are significantly lower than the potentially harmful doses.³⁴

The Australian case should be mentioned as an example of the limited efficacy of iodine prophylaxis through iodine-enriched food for ID correction during pregnancy and lactation.^{70,71} Changes in livestock farming practices in Australia had resulted in the reappearance of moderate ID, with a high risk of increased severity for infants and women during pregnancy and breast-feeding, and the use of IS in bread manufacturing became mandatory in 2009. In 2010, the Australian government recommended the use of IKS (150 µg/day) to all pregnant and lactating women, after recognizing that mandatory bread iodination had not been able to meet the increased iodine requirements during pregnancy and lactation. Two very recent studies^{72,73} show that only women who took iodine-containing supplements during pregnancy and lactation achieved urinary iodine levels in the iodine sufficiency range. It is estimated that iodine-containing supplements are used by 40% of pregnant Australian women,⁷¹ as compared to 20% of pregnant women in the United States,⁶⁹ which emphasizes the importance of adequate public health strategies for ID correction during pregnancy and lactation.

Conclusions

The correction of ID in Spain achieved in 2004, mainly through silent or uncontrolled iodine prophylaxis, has failed to decrease the risk of ID in pregnant and lactating women. A similar situation is found in virtually all Spanish regions. The proven lack of efficacy of iodine prophylaxis through iodine intake in the food chain to correct ID in the pregnant population, despite the fact that Spain was already among the countries with an optimum iodine nutrition, prompted the recommendation of IKS use to all pregnant and lactating women from 2005. The lack of substantial changes in dietary habits aimed at eradicating ID, as well as its proven persistence in pregnant Spanish women, are strong arguments not only not to advise against universal IKS, but also to promote additional public health strategies to definitively correct this deficiency during pregnancy and lactation. Although median urinary iodine levels in the non-pregnant Spanish population are higher than 100 µg/L, mean IS consumption in Spanish households, still very far from the 90% established by the WHO, advises maintenance of the recommendation to use iodine supplements during pregnancy and lactation.¹²

The benefits of iodine supplementation in pregnant women with moderated ID clearly outweigh its limited potential harmful effects on maternal–fetal health reported in the worldwide scientific literature. The demand by some authors for greater evidence of the benefits of IKS in moderate ID will probably be difficult to meet in the coming years because iodine-sufficient populations will increase and iodine-deficient populations will decrease all over the world.⁶¹ On the other hand, the conduct of placebo-controlled intervention studies where some pregnant women were deprived of any iodine provision (both

as IS and IKS) would be unethical because of the proven increase in iodine requirements during pregnancy and lactation. Many international organizations and scientific bodies⁶⁹ have therefore made recommendations for increasing iodine contents in the diet of pregnant and lactating women.

It should finally be stressed that although the final recommendations of the BW¹ state that universal IKS is currently not warranted, all speakers (a representative of the Ministry of Health and four representatives of different Spanish autonomous communities) but one recommended either the routine use of IKS in all pregnant women or its use when there is no certainty of an adequate iodine provision, which represents in practice universal, rather than individualized, supplementation. The final recommendation in the BW regarding something so important for the health of the pregnant Spanish population is surprising because it does not appear to be the expected agreed statement of a homogeneous position of the BW attendants on iodine supplementation during pregnancy and lactation.

Based on the foregoing, the Working Group on IDD-TD sets out the following conclusions:

- (1) Although the WHO considers Spain as an iodine-sufficient country, ID persists in most pregnant women.
- (2) In recent years, silent and uncontrolled iodine prophylaxis has been performed in Spain. Based on international experiences showing the limited sustainability of this form of iodine prophylaxis, there is a high risk of the reappearance of ID in Spain.
- (3) Public health strategies should be designed to guarantee a controlled and sustained increase in iodine intake in the whole population, and especially in the groups most sensitive to ID, such as infants and women during pregnancy and lactation. Such strategies should include institutional programs that guarantee the availability of adequately iodinated salt to all the population and that promote its consumption, without excluding the possibility of extending the use of IS to the food industry. This will be the only way to ensure in the future the adequate replenishment of thyroid iodine deposits before pregnancy in women of childbearing age.
- (4) No screening methods allowing for the identification of the individual risk of experiencing ID during pregnancy are currently available. Therefore, selective IKS only for women whose previous or future dietary habits suggest the possibility of ID, as recommended by the BW, may place the vast majority of pregnant Spanish women at a real risk of ID.
- (5) In an attempt to achieve the goal that the vast majority of the pregnant Spanish population has an adequate iodine nutritional status, our Working Group on IDD-TD maintains the explicit recommendation of the prescription of potassium iodide before pregnancy, if possible, and during pregnancy and lactation.
- (6) Our group urges the continued advance, always respecting ethical postulates and aiming at therapeutic benefits, in our understanding of the maternal–fetal impact of ID and of the optimum measures to eradicate iodine deficiency in Spain.

Annex 1. List of members of the Working Group on Iodine Deficiency Disorders and Thyroid Dysfunction of the Spanish Society of Endocrinology and Nutrition who endorse the following document

Arena, Jose; Ares, Susana; Bandrés, María Orosia; Berbel, Pere; De la Vieja, Antonio; Donnay, Sergio; García, Eduardo; Gentil, Alfonso; Lucas, Anna; Muñoz, Jose; Menéndez, Edelmiro; Millón, María del Carmen; Moll, Gracia; Pineda, Jose Javier; Puig-Domingo, Manel; Riestra, María; Santiago, Piedad; Tortosa, Frederic; Velasco, Inés; Vich, Francisca; Wengrowicz, Silvia.

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