Iodine status, thyroid and pregnancy

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Abstract

Iodine is an essential trace element for life. Its biological effects is due to the fact that iodine is an integral part of the thyroid hormones, and thus plays a crucial role in fetal organogenesis, and in particular in brain development. This takes place during early gestation and involves delicate targeting throughout the central nervous system. Iodine deficiency in pregnant women - defined as a median of urinary iodine excretion of less than 150 µg/L in pregnant and lactating women - is the leading cause of preventable mental retardation, affecting as many as 2 billion people –35.2%- at the beginning of the new century. Europe has a very high prevalence of iodine deficiency in the general population, with nearly 50% of the 600 million people in Western and Central Europe having insufficient iodine intake. Recent Studies involving pregnant women indicate that in Belgium, Poland, France, Italy, Denmark, Turkey, Portugal, and some regions of Spain, iodine deficiency has been detected. Iodine deficiency is often associated with a deficiency of other nutrients such as Selenium, Iron or Vitamin A, contributing to a worsening of the biological effects of iodine deficiency. Prevention of fetal iodine deficiency is feasible, provided that iodine supplements of 200-300 µg/day to the mother are given both, before and throughout gestation and continued through lactation. The presence of other micronutrients deficiencies cannot be forgotten, and a combined multi-supplement approach covering all these nutritional needs, seems the best practice in pregnancy.
Introduction

In this manuscript we will review some epidemiological data on the status of iodine deficiency in pregnant women in Europe, the current recommendations regarding when and how to supplement with iodine in pregnant women, and finally, what are the reported data related to the consequences for the progeny when iodine supplements are given to the mother during pregnancy. The consequences of iodine deficiency are due to the fact that iodine is an integral part of the thyroid hormones. Since the first reports by Pharoah in the 70s \(^1\) and Thilly \(^3\), the last three decades have brought to the fore both epidemiological and experimental data confirming that defective maternal iodine input, leading to insufficient maternal production of thyroxine during pregnancy is associated to a variety of tissue damage in the progeny. The spectrum of severity ranges from relatively mild neurocognitive defects to severe alterations of mental function in those lesions best documented relating to iodine related maternal hypothyroxinemia. We now know from experimental studies that these functional defects have demonstrable underlying structural lesions of an irreversible nature and originate in early pregnancy at the time of fetal organogenesis \(^4\)\(^-\)\(^6\). Most of the clinical data found in the literature are derived from studies performed in areas of extreme iodine deficiency or in cases of untreated maternal hypothyroidism; however, it has been demonstrated that even a moderate lack of iodine can have detrimental and irreversible consequences for the fetus, and therefore should be understood as a continuum in which the milder forms could be defined as fetal iodine deficiency disorder, and are currently neglected or ignored in the general medical practice \(^7\).

Iodine deficiency - defined as a median of urinary iodine excretion of less than 100 µg/L for general population and 150 µg/L in pregnant and lactating women \(^8\)\(^,\)\(^9\) - is the leading cause of preventable mental retardation, affecting as many as 1.6 billion people -29% of world population- according to WHO data in 1990 \(^10\), increasing to approximately 2 billion people –35.2%– at the beginning of the new century. These data include 285 million school-age children in 2006 \(^11\) and indicate that the WHO’s goal of avoiding new cases of iodine deficiency disorders by the year 2000 has not been accomplished; and the sad story is that even if this problem can be prevented with very cost-effective and efficient programs ensuring a sufficient iodine supply provided to the mother before and during pregnancy, the current achievements are far from what has been an international commitment by many governments \(^12\), including those of the European Union.

For a long time, the idea that the principal factor accounting for impaired fetal neurologic development was maternal hypothyroidism –defined as a state of increased serum TSH- has prevailed \(^13\)\(^,\)\(^14\). In the last decade, the progress in thyroid research has allowed a more in-depth knowledge of maternal, placental and fetal thyroid hormones interrelationships \(^15\), the trafficking of thyroxine through the placenta, as well as the full characterization of the ontogeny of thyroid hormone receptors in the placenta and embryonic tissues \(^16\). All this information taken together, has given the basis for a better physiopathological understanding of the diversity of clinical expression of endemic cretinism, or in modern terminology, fetal iodine deficiency disorder. This has at times led to confusion, being both,
the neurologic cretinic and the myxedematous forms – with considerable overlap in between – explained and driven by the timing and severity of pre and postnatal iodine deficiency. This confirms the crucial role of maternal euthyroxinemia in early pregnancy as a prerequisite for a normal embryonic development 17.

**Epidemiology of iodine deficiency in pregnant women in Europe**

In 2003 about 2000 million people were currently estimated to be iodine deficient worldwide (35.2% of the entire world population) 11. Paradoxically, Europe, which has been thought to be free of iodine deficiency disorders and has been leading the research in the field, has in fact the highest prevalence of iodine deficiency, with nearly 50% of the 600 million people in Western and Central Europe having an insufficient iodine intake 18, defined as urinary iodine <100 µg/L 19. Northern and Southern America are at the other end of the spectrum, with a prevalence of iodine deficiency of less than 10%. According to very recent studies which have examined the European countries where iodine status is threatening pregnancy outcome, we realize that the list is long and includes (Table 1): Belgium, Poland, France, Italy, Denmark, Turkey, Portugal, and some regions of Spain.

<table>
<thead>
<tr>
<th>*Iodine Nutrition</th>
<th>publication year</th>
<th>N</th>
<th>S/C</th>
<th>Trimester&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Median of urinary iodine</th>
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<tr>
<td>Germany&lt;sup&gt;11&lt;/sup&gt;</td>
<td>1996</td>
<td>89</td>
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<td></td>
<td></td>
<td>89</td>
<td>11 P</td>
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<td>50 µg/g cr</td>
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<td>32</td>
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<td></td>
<td></td>
<td>32</td>
<td>S</td>
<td>2</td>
<td>170 µg/day</td>
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<tr>
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<td>32</td>
<td>S</td>
<td>3</td>
<td>145 µg/day</td>
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<tr>
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<td>511</td>
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<tr>
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<td></td>
<td>(León)&lt;sup&gt;19&lt;/sup&gt;</td>
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<td></td>
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<td>120 µg/L</td>
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<td></td>
<td></td>
<td>2004</td>
<td>520</td>
<td>S</td>
<td>1</td>
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<td></td>
<td></td>
<td></td>
<td>2</td>
<td>77 µg/L</td>
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<td>520</td>
<td>S</td>
<td>3</td>
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<td>520</td>
<td>S</td>
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<td>520</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>(Madrid)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>2006</td>
<td>112</td>
<td>C</td>
<td>2-3</td>
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<tr>
<td></td>
<td>(Alicante)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>2007</td>
<td>104</td>
<td>S</td>
<td>1</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>2</td>
<td>140 µg/L</td>
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<tr>
<td></td>
<td>(Bizkaia)&lt;sup&gt;20&lt;/sup&gt;</td>
<td>2007</td>
<td>2191</td>
<td>S</td>
<td>1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>1401</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>(Extremadura)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>2008</td>
<td>761</td>
<td>S</td>
<td>1</td>
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<td></td>
<td></td>
<td>362</td>
<td>S</td>
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<td></td>
<td></td>
<td>362</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>(Val Aran)&lt;sup&gt;22&lt;/sup&gt;</td>
<td>2008</td>
<td>35</td>
<td>S</td>
<td>1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>32</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>(Valencia)&lt;sup&gt;23&lt;/sup&gt;</td>
<td>2010</td>
<td>530</td>
<td>C</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>C</td>
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<tr>
<td></td>
<td>(Gulpuzcua)&lt;sup&gt;24&lt;/sup&gt;</td>
<td>2010</td>
<td>126</td>
<td>C</td>
<td>1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>475</td>
<td>C</td>
</tr>
<tr>
<td>(Sabadell)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>2010</td>
<td>122</td>
<td>C</td>
<td>1</td>
<td>97 µg/L</td>
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In different Spanish studies performed in Catalonia, while most of schoolchildren\textsuperscript{58} and general population\textsuperscript{59} had acceptable iodine nutrition, about half pregnant women of this region had an insufficient iodine supply\textsuperscript{60,61}, and in some particular places of Catalonia, the proportion of women showing less than 150 µg/L of urinary iodine has shown to be up to 74\%\textsuperscript{62}. In these Catalan studies, the prevalence of maternal hypothyroxinemia ranged between 1.4 and 4.2\%\textsuperscript{63}. Similar data have been found in other different regions of Spain\textsuperscript{27,29}. These and other studies indicate that in countries with an apparently acceptable iodine status, in pregnancy, the dietary iodine supply is insufficient for covering gestational requirements, and therefore, other strategies as, i.e., preconceptional oral supplementation with potassium iodide or others, are needed for solving the problem, although from epidemiological surveys, this practice less 15-50\% of pregnant women in Europe\textsuperscript{64}.

### When and how for a safe iodine supplementation in pregnancy

Without doubt, the best practice would be to ensure a sufficient replenishment of thyroid iodine stores before pregnancy, but as mentioned, this ideal situation is far from being a reality, and mostly in Europe. Up until now an early (or not so early) supplementation during pregnancy has usually been the case. The addition of iodine during gestation has not always been accepted and is not general practice by the obstetric community; moreover, it has even been questioned if not suspected of being...

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<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Mean Urinary Iodine (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>1990</td>
<td>C</td>
<td>230</td>
<td>58</td>
</tr>
<tr>
<td>Poland</td>
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<td>C</td>
<td>46</td>
<td>35</td>
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<td>Denmark</td>
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<td>C</td>
<td>26</td>
<td>51</td>
</tr>
<tr>
<td>France</td>
<td>1997</td>
<td>S</td>
<td>306</td>
<td>50</td>
</tr>
<tr>
<td>Ireland</td>
<td>2009</td>
<td>S</td>
<td>38</td>
<td>135</td>
</tr>
<tr>
<td>Italy</td>
<td>2002</td>
<td>C</td>
<td>67</td>
<td>74</td>
</tr>
<tr>
<td>Italy</td>
<td>2008</td>
<td>C</td>
<td>51</td>
<td>74</td>
</tr>
<tr>
<td>Turkey</td>
<td>1995</td>
<td>C</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>Turkey</td>
<td>2005</td>
<td>C</td>
<td>18</td>
<td>143</td>
</tr>
<tr>
<td>Turkey</td>
<td>2004</td>
<td>C</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Portugal</td>
<td>2009</td>
<td>S</td>
<td>136</td>
<td>65</td>
</tr>
<tr>
<td>Portugal</td>
<td>2009</td>
<td>S</td>
<td>128</td>
<td>57</td>
</tr>
<tr>
<td>Portugal</td>
<td>2009</td>
<td>S</td>
<td>119</td>
<td>70</td>
</tr>
</tbody>
</table>

\*Current classification of countries based in iodine nutrition\textsuperscript{19}  
\*S/C, sequential (S) or cross-sectional study (C)  
\*Timing of urinary iodine determination. PP, postpartum. Adapted from Glinoer (2003)\textsuperscript{55}  
\*Mean of urinary iodine
harmful for the progeny. Eight different trials aiming to study the effects of iodine supplementation early during pregnancy have been performed in Europe in the last two decades, including about 700 women in which iodine was given at a dose ranging 50-300 μg/day. In all these studies, median urinary iodine increased about two to three-fold and thyroid volume virtually did not change in treated women, while in 20-30% of the control population an increase in thyroid volume was detected by ultrasonography. Overall, treatment had no effect on maternal TSH and thyroglobulin, and cord thyroglobulin levels were significantly lower in the treated groups. No significant differences were found between groups comparing maternal or cord T4, T3, and FT4. How ever, in the studies in which the amount of iodine given was the highest, FT4 was lower when compared to the control groups in the third trimester, as in the study by Velasco, but also, FT4 decrease in comparison to first trimester values was less. Fetal TSH in this last study was higher in the babies in which the mothers were supplemented in comparison to those who were not, but their neuropsychological development was better according to the Bayley scales scores when compared to the non-supplemented control group. In general, for the newborn, most data suggest that supplementation is safe, although three of the mentioned studies showed higher newborn TSH levels –albeit within normal values- when supplementation was reported. Until now, the interpretation of this event has usually been seen as potentially harmful for the baby, but it may not be so deleterious if we consider that in two of the studies neurodevelopmental scores were better in these children and particularly in those where their mothers were supplemented earlier in their pregnancies. Considering this point, the time when iodine is introduced during pregnancy seems to be very important; in the study also performed in Spain by Berbel, neurocognitive development assessed by the Brunet-Lézine was better in the kids of mothers in which supplementation was started at 4-6 weeks of gestational age in comparison to those where supplements started at 12-14 weeks of gestation or no supplement was given. This implies that the therapeutic window is restricted to the very early pregnancy, and therefore if a pregnancy is planned, the time of trying to become pregnant is the ideal moment in which to replenish the maternal iodine thyroid stores. Also an analysis should be performed as soon as the woman is aware that she is pregnant.

The usual form of iodine supplements are potassium iodide tablets or iodine-containing prenatal multivitamin preparations. Another option is i.m. iodized oil that has been used in South America; it is safe and its single dose is easy to administer, and may provide constant blood iodine levels. According to the surprisingly low compliance of some very well established preventive programmes, such as oral folic acid supplementation, which is followed just by 7-42% pregnant women in some European studies, this latter possibility of using a single and simple depot administration of i.m. iodized oil injection prior to conception, seems to be a reasonable solution in a potentially non-compliant population.
Questions remaining to be answered in iodine supplementation for pregnant women

Despite all data previously commented, a substantial debate is still going on the dose to be given, and if an undetected thyroid disease in the mother maybe influenced by iodine supplementation. In relation to the dose to be used, no adverse effects of 50–300 µg daily iodine supplement have been documented in moderately iodine-deficient pregnant women. Theoretically, it is possible that doses higher than 500 µg/day of supplemental iodine could result in fetal hypothyroidism. The ability to escape from the acute Wolff-Chaikoff effect, and therefore to avoid iodine-induced hypothyroidism, seems not fully active until around 36 wk of gestational age \(^{80,81}\), and therefore the World Health Organization has stated that daily iodine intake greater than 500 µg/day may be excessive in pregnancy \(^{82}\); the European Food Agency has defined a similar limit of 600 µg/day; finally, the U.S. Institute of Medicine considers the safe upper limit for daily iodine intake as 1100 µg/day in pregnant women \(^{83}\), indicating that the safe upper limit seems to be quite high. Probably more studies are needed to better define this issue, but what is certain is that most women supplemented with 200-300 µg/day will reach a sufficient replenishment of their thyroid stores safely, and if this is done before conception the potential maternal and fetal Wolff-Chaikoff effects maybe avoided.

In the case that a pregnant woman is discovered to have an inhibited TSH in the first trimester, iodine supplementation should be maintained, although it is recommended to perform a clinical follow-up with measurement of total and free T4. It has to be remembered that TSH may not be the best parameter of thyroid function to be used during the first trimester as it decreases physiologically under the effect of increasing hCG concentrations. The same applies for those women having Graves disease in remission; and it is unlikely that unfavourable effects of 200-300 µg/day of iodine may happen. This should be clearly differentiated from a real pharmacological dose of iodine, i.e, the one given in the treatment with amiodarone. Furthermore, if a woman having an active Graves disease or a toxic multinodular goiter becomes pregnant, iodine supplementation should not necessarily be stopped if the case is treated with the usual antithyroidal drugs, and the follow-up should not be different to usual practice \(^{84}\). In fact Graves disease tends to remit during the second trimester, regardless if iodine is or is not included in the pregnancy supplementation protocol. It has been argued that patients under replacement thyroxine treatment because of previous hypothyroidism, might not require iodine supplements; if we take into account that levothyroxine supplies 65.3 µg of iodine/100µg of thyroxine, it is clear that the iodine released during thyroxine metabolism is insufficient for the fetus, which then needs iodine during the second half of the pregnancy for synthesising its own thyroxine \(^{17}\).

In all the published data there was no increase in maternal thyroid autoimmunity, or in the prevalence or severity of post-partum thyroiditis \(^{85}\), therefore even if a theoretical risk existed, the iodine requirements of the fetus and its benefits, justify the administration of potassium iodine to the mother. Finally, most of the studies seem to agree that iodine supplementation should be continued until the end of lactation, as the iodine content of maternal milk is enriched \(^{64,86}\).
Iodine and other Nutrients

Iodine deficiency is often associated with deficits of other nutrients such as Selenium (Se), Iron (Fe) or Vitamin A (Vit A) \(^{87-89}\). Se is a major constituent of enzymes such as glutathione peroxidise (GPx), thioredoxin reductase (TxnRd) and the iodothyronine deiodinases (D1O1- O3) which are essential for thyroid hormonogenesis and metabolism \(^{90}\). Concurrent deficiencies of one or more of these substances can intensify the effects of iodine deficiency. For example, in combined iodine and Se deficiency there is a failure to utilise H2O2 for thyroid hormonogenesis with build up of cytotoxic products leading to myxedematous cretinism \(^{91}\). Giving Se alone can exacerbate the hypothyroidism due to increased deiodination of stored T4. In this situation it is important to resolve the iodine deficiency before administering Se \(^{87,91}\). Deficiencies of Fe and Vit A are common in pregnancy. A combination of Fe and I deficiency can result in decreased thyroid hormone production as Fe is an important component of TPO \(^{92}\). Fe deficiency may block a child’s ability to use iodide. Iodide prophylaxis may be of no use if Fe is not given simultaneously \(^{93}\). Another aspect of the Fe/I story is the increased Fe requirement in pregnancy. Fe deficiency may contribute to the increased TSH seen in late pregnancy \(^{94}\). Vit A deficiency has been shown to be associated with increased TSH while high doses of Vit A can decrease production of the promoter on the TSHb subunit gene \(^{88}\). These findings strongly support the need for combined approaches for correcting nutritional deficiencies \(^{92}\).

In summary, iodine status of pregnant women is clearly suboptimal in many regions of Europe, and iodine-containing supplements have a beneficial impact or are at least are safe for the iodine and thyroid status of both the mother and the newborn. Pregnant women in these regions, if not adequately covered by iodized salt or even using iodized salt, should be supplemented with iodine in most cases, ideally during the preconceptional situation, or during early (as soon as possible) pregnancy and lactation in order to ensure a maximal normal neurodevelopment of their children. The presence of the others nutritional deficiencies cannot be forgotten.

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