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**Review**

**Iodine Deficiency in Pregnancy: The Effect on Neurodevelopment in the Child**

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**Abstract:** Iodine is an integral part of the thyroid hormones, thyroxine (T₄) and triiodothyronine (T₃), necessary for normal growth and development. An adequate supply of maternal free T₄ (fT₄), generated in the brain from T₃, is needed by the fetus for thyroid hormone dependent neurodevelopment, which begins in the second half of the first trimester of pregnancy. Around the beginning of the second trimester the fetal thyroid also begins to produce hormones but the reserves of the fetal gland are low, thus maternal thyroid hormones contribute to total fetal thyroid hormone concentrations until birth. In order for pregnant women to produce enough thyroid hormones to meet both her own and her baby’s requirements, iodine intake needs to increase by 50%. If this does not occurs, the mother may become iodine deficient, and subsequently the fetus. In iodine deficiency, hypothyroxinemia (i.e. low maternal fT₄) results in damage to the developing brain, which is further aggravated by hypothyroidism in the fetus. The most serious consequence of iodine deficiency is cretinism, characterised by profound mental retardation. There is unequivocal evidence that severe iodine deficiency in pregnancy impairs brain development in the child. However, only two intervention trials have assessed neurodevelopment in children of moderately iodine deficient mothers finding improved neurodevelopment in children of mothers supplemented earlier rather than later in pregnancy; both studies had methodological limitations. There is a need for well-designed trials to determine the effect of iodine supplementation in moderate to mildly iodine deficient pregnant women on neurodevelopment in the child.

**Keywords:** iodine; pregnancy; child; cretinism; neurodevelopment
1. Introduction

Despite considerable progress over the last 25 years, iodine deficiency is still one of the most common micronutrient deficiencies in the world today. Iodine deficiency results in a wide spectrum of adverse consequences throughout the lifecycle. Of greatest concern is the effect of iodine deficiency on the developing brain. The most serious effect of iodine deficiency is cretinism, which occurs in women who are severely iodine deficient during pregnancy. The promotion of iodised salt by the World Health Organization (WHO) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) has helped to alleviate endemic cretinism in many parts of the world. Attention is now turning to the adverse effects of moderate and mild iodine deficiency in pregnancy. Although iodine deficiency in pregnancy will affect both the mother and the child, little attention has been paid to the consequences of iodine deficiency on maternal health. This review will describe the role iodine plays, via thyroid hormones, in the development of the brain from conception to birth and present evidence of the impact of severe, moderate, and mild iodine deficiency in pregnancy on neurodevelopment in the child.

2. The Role of Thyroid Hormones in Fetal Brain Development

Iodine is essential for the production of the thyroid hormones, the prohormonethyroxine (T₄) and the active form 3,5,3’-triiodothyronine (T₃), which are vital for normal growth and development particularly of the brain and central nervous system. Maternal thyroid hormones are found in the embryonic cavities ~4 weeks after conception despite the placenta acting as a barrier designed to prevent excessively high levels of fT₄ and T₃ from reaching the fetus before they are needed[1,2]. Thyroid hormones are not believed to play a role in very early fetal development as studies have shown that nuclear receptors for thyroid hormones are only present in the fetal brain from ~8-9 weeks gestation reaching adult levels by 18 weeks gestation[2]. Before midgestation, the mother is the only source of cerebral T₃, which is generated locally by type II 5’iodothyroninedeiodinase activity from maternal free T₄ (fT₄). The first stage of thyroid hormone dependent neurodevelopment begins in the second half of the first trimester and includes neuronal proliferation and the onset of neuronal migration in the cerebral cortex, hippocampus and medial ganglionic eminence, the latter processes starting in the first trimester and continuing into the early part of the second trimester; this stage depends on an adequate supply of maternal fT₄[2]. Towards the end of the first trimester, in response to high concentrations of placental human chorionic gonadotropin (hCG), there is a surge in maternal T₄ and a decline in thyroid stimulating hormone (TSH), a mechanism thought to ensure that fT₄ is supplied to the fetus during this period[2,3]. Around the beginning of the second trimester the fetal thyroid begins to produce hormones, however, the full development of the pituitary-portal vascular system in the fetus does not occur until ~18-20 weeks gestation[1]. The second stage of thyroid hormone neurodevelopment includes such processes as neurogenesis, neuron migration, axonal growth, dendritic branching and synaptogenesis, glial cell differentiation and migration, and the onset of myelination. The third stage occurs after birth [2]. Although the concentration of T₄ in the fetus increases as gestation progresses, the reserves of the fetal gland are low and the gland itself does not fully mature until birth, thus maternal thyroid hormones continue to contribute to total fetal thyroid...
hormone concentrations until birth. It is no surprise, therefore, that low fT₄ occurs in premature babies as they are deprived of a maternal supply, and this may partly account for some of the developmental delay often apparent in such children[2].

In order for pregnant women to produce enough thyroid hormones to meet fetal requirements, iodine intake needs to increase by 50%. If this does not occur, then the mother may become iodine deficient, and subsequently the fetus. The mother and the fetus, however, respond differently to this situation, with the mother remaining euthyroid and fetus becoming hypothyroid[3]. Iodine deficient pregnant women remain euthyroid for two reasons. Firstly, the increase in maternal fT₄ that occurs at the end of the first trimester in response to hCG depresses the concentration of maternal TSH. Secondly, the maternal thyroid gland responds to a state of relative iodine deficiency by invoking the autoregulatory mechanisms available to the mother do not take place in the fetus because the fetal thyroid gland has not fully matured. Consequently, in the fetus there is a decreased synthesis and secretion of T₄ and T₃, and an increase in the concentration of TSH, resulting in fetal hypothyroidism[3]. This explains why neonatal TSH is used as an index of iodine deficiency in a population.

A number of studies have been undertaken in women living in areas of adequate iodine status who have low T₄ concentrations in pregnancy, usually as a result of thyroid disease. In a study of Dutch pregnant women with fT₄<10th percentile during pregnancy it was found that their children had poorer psychomotor development at 10 months of age [4], and again at one and two years of age [5] than children whose mothers had higher T₄ levels in pregnancy. A more recent study found that pregnant Dutch women with fT₄<10th percentile at 12 weeks gestation had infants with significantly lower orientation scores as assessed using the Neonatal Behavioural Assessment Scale than mothers with fT₄ between the 50th and 90th percentiles [6]. Zoeller and Rovet discuss the role of thyroid hormones on brain development using data obtained from studies of maternal hypothyroidism andmaternal hypothyroxaemia[7]. They suggest that decreased thyroid hormones early in pregnancy may cause problems in visual attention, visual processing, and gross motor skills, while a lack of thyroid hormones later in pregnancy results in further problems with visual skills, slower processing speeds, and fine motor skills. These observational studies provide evidence that variations in maternal hormones influence normal brain development. It is important to remember that the cause of abnormal thyroid hormone concentrations in the studies discussed in this paragraph is usually the result of thyroid dysfunction in the mother, and not from iodine deficiency per se. Nonetheless, the assumption made by scientists working in this area is that, regardless of the cause, the functional consequences of abnormal thyroid hormones on neurodevelopment in the fetus are the same.

In summary, it is clear that low concentrations of maternal T₄, in particular, can hinder the development of the fetal brain. If severe to moderate iodine deficiency is present, the damage to the developing brain in the first half of pregnancy is caused by hypothyroxinemia of a euthyroid mother, which can continue in the second half of pregnancy and is then further aggravated by hypothyroidism in the fetus. It is uncertain, however, if this occurs in situations of moderate or mild iodine deficiency.
3. Determining the Severity of Iodine Deficiency in Pregnancy

One of the problems in this area of research is the difficulty in determining the severity of iodine deficiency in pregnant women. The mostly commonly used index for assessing iodine status in a population is the median urinary iodine concentration (MUIC) as determined from a casual or spot urine sample. A MUIC >100 µg/L is indicative of adequate iodine status in children, men and non-pregnant women, with a MUIC of 50-99 µg/L, 20-49 µg/L, and <20 µg/L indicating mild, moderate, and severe iodine deficiency, respectively[8]. In 2007, WHO recommended a MUIC >150 µg/L be used in pregnancy, however, no cut-offs for the severity of iodine deficiency in pregnancy have been proposed [8]. Furthermore, given the large variability in the iodine concentration of casual urine samples, the iodine status of an individual cannot be determined from a urine sample. In other words, a pregnant woman cannot be classified as iodine deficient based on her urinary iodine concentration [9].

Pregnant women can have their thyroid hormones measured, with TSH and fT$_4$ typically used to define subclinical hypothyroidism (TSH >97.5$^{th}$ percentile, fT$_4$ in normal reference range), overt hypothyroidism (TSH >97.5$^{th}$ percentile and fT$_4$<2.5$^{th}$ percentile), and hypothyroxinemia (TSH in normal reference range, fT$_4$<2.5$^{th}$ percentile) [10]. There is debate as to whether all pregnant women should be screened for abnormal thyroid hormone concentrations in the first trimester. Changes in thyroid hormones can be caused by a variety of factors such as thyroid disease, and is not specific to iodine deficiency. Indeed, WHO do not recommend the routine use of TSH, T$_4$ and T$_3$ for monitoring iodine status in the adult population as these tests are relatively insensitive in moderate to mild iodine deficiency; MUIC provides sufficient information to assess iodine status in these groups. However, because of the importance of maternal thyroid hormone concentrations for normal fetal brain development, the establishment of trimester specific international reference ranges for thyroid hormones in iodine sufficient and deficient pregnant women could be useful in identifying at-risk women.

4. The Effect of Severe Iodine Deficiency in Pregnancy on Neurodevelopment in the Child

Severe iodine deficiency exists when more than 30% of children have goitre, a MUIC < 20 µg/L, and the presence of cretins in a community, born to women severely iodine deficient in pregnancy. Cretinism is always associated with a significant impairment in mental function and/or defects in hearing, speech, stance, gait, hypothyroidism and growth [11]. There are two types of cretinism, although the symptoms of both types can sometimes be seen in the same individual. The more common form of cretinism is neurological cretinism, characterised by mental retardation, deaf mutism, squint, spastic diplegia, and disorders of the stance and gait. The less common form of cretinism is called myxoedematous or hypothyroid cretinism and is characterised by less severe mental retardation, dwarfism, hypothyroidism, and a variety of other physical symptoms such as coarse and dry skin, a husky voice, and delayed sexual maturation. Normal IQ in a population is 100, while the IQ of cretins has been reported to be around 30 [12]. In areas with endemic cretinism, around 5-15% of non-cretinous children will have impaired mental function with an IQ of 50-69; these children are sometimes referred to as “sub-cretins”[11]. Although factors such as the presence of goitrogens in the diet, thyroid auto immunity, and interactions with other trace elements such as selenium have been
postulated to have a role in the development and type of cretinism, the overarching reason for cretinism is severe iodine deficiency in the mother[13]. The importance of adequate dietary iodine in preventing cretinism was highlighted in the 1960s in a large trial of 165,000 people living in a part of Papua New Guinea with severe iodine deficiency and endemic cretinism[14]. In this study, families were allocated to iodised oil or placebo and subsequent studies found that an injection of iodised oil before conception or in early pregnancy reduced the incidence of cretinism and improved the motor and cognitive functions of children compared with those families who received the placebo. Another study undertaken in 1990 in a remote province in China with endemic cretinism examined the effect of iodised oil given during pregnancy on neurological outcomes. Children of mothers given iodine earlier in pregnancy had improved cognitive outcomes compared to mothers given iodine later in pregnancy at both two years [15] and again when children were school-aged [16]. A meta-analysis of Chinese studies reported a decrease of 8.7 IQ points in children living in severely iodine deficient areas whose mothers were untreated in pregnancy compared to supplemented mothers also living in severely iodine deficient areas [17].

It is unequivocal that severe iodine deficiency in pregnancy results in significant impairment in cognition in the child. It has been suggested that cretinism is at the far end of a spectrum of effects that iodine deficiency can have on the central nervous system, and that varying degrees of intellectual impairment can occur across this spectrum concordant with the degree of iodine deficiency. This theory has yet to be substantiated.

5. The Effect of Moderate to Mild Iodine Deficiency in Pregnancy on Neurodevelopment in the Child

A number of clinical trials published between 1991-2002 in pregnant women living in regions with moderate deficiency are summarized in Table 1 [18-25]. Daily iodine supplements ranging from 100 to 300 µg of iodine were taken by women in their first or second trimester of pregnancy. The majority of the studies showed that iodine supplements were effective in alleviating aspects of iodine deficiency in supplemented women compared to those taking the placebo. With regard to these studies, iodine expert Dr Michael Zimmermann wrote “…because none of the trials measured long-term clinical outcomes, such as maternal goiter or infant development, the potential adverse effects of mild-to-moderate iodine deficiency during pregnancy remain unclear” [26]. In 2009, two randomised trials were published investigating the effect of iodine supplementation in moderately iodine deficient pregnant women supplemented on neurodevelopment in their children. Berbel et al recruited three groups of pregnant women living in Spain at different phases of gestation (i.e. 4-6 wks, 12-14 wks, and near term), who had T₄ concentrations <10th percentile at recruitment but normal TSH throughout pregnancy, and supplemented them with 300 µg of iodine until the end of lactation [24]. When the children were 18 months old, the development quotient of children in mothers supplemented in the first trimester (i.e. 4-6 wks) was significantly higher than that of children whose mothers received supplements from 12-14 wks gestation and near term. A limitation of this study is the small numbers of children tested, with less than 20 children in each of the three groups. Furthermore, these women were specifically selected because they had low fT₄ throughout pregnancy; whether such a result would be found in iodine deficient pregnant women with fT₄ concentrations >20th percentile is not known. A second Spanish
study by Velasco et al found that children of mothers supplemented with iodine in the first trimester had higher psychomotor development scores than children from mothers who did not start supplementation until the last month of pregnancy [25]. Although some socio-demographic variables were collected in this study with no significant differences between the two groups, the children in the supplemented group had mothers and fathers who were better educated and were more likely to be an only child. These and other social characteristics, such as household income, together could influence neurodevelopment and explain the results found. Furthermore, children were tested at different ages in this study (5.5 months vs 12.4 months). Finally, both studies were not randomised, double-blind, placebo-controlled trials, and although they suggest that neurodevelopment in the child may be adversely affected by moderate iodine deficiency, they are not definitive.

Table 1. Intervention studies investigating the effect of iodine supplementation in pregnancy.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Country</th>
<th>n</th>
<th>Methods</th>
<th>Baseline UIC µg/L</th>
<th>Effect on child neurodevelopment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romano et al (1991)</td>
<td>Italy</td>
<td>35</td>
<td>1st trimester randomised to 0 or iodine supplement (120-180 µg I/day).</td>
<td>37</td>
<td>Not assessed.</td>
</tr>
<tr>
<td>Pederson et al (1993)</td>
<td>Denmark</td>
<td>54</td>
<td>17-18 weeks gestation randomised to 0 or 200 µg I/day.</td>
<td>55</td>
<td>Not assessed.</td>
</tr>
<tr>
<td>Glinoer et al (1995)</td>
<td>Belgium</td>
<td>120</td>
<td>Euthyroid women with signs of excessive thyroid stimulation randomised to 0 or 100 µg I/day.</td>
<td>36</td>
<td>Not assessed.</td>
</tr>
<tr>
<td>Liesenkötter et al (1996)</td>
<td>Germany</td>
<td>118</td>
<td>10-12 weeks gestation given 300 µg I/day vs untreated women.</td>
<td>53</td>
<td>Not assessed.</td>
</tr>
<tr>
<td>Nohr and Laurberg (2000)</td>
<td>Denmark</td>
<td>144</td>
<td>Retrospective allocation at term based on self-reported intake of supplements containing 150 µgI /day</td>
<td>Not given.</td>
<td>Not assessed.</td>
</tr>
<tr>
<td>Antonangeli et al (2002)</td>
<td>Italy</td>
<td>86</td>
<td>Healthy women 10-16 weeks gestation randomised to 50 or 200 µg I/day.</td>
<td>74</td>
<td>Not assessed.</td>
</tr>
<tr>
<td>Berbel et al (2009)</td>
<td>Spain</td>
<td>96</td>
<td>Mildly hypothyroxinemic women with normal TSH until term given 200 µg I/day until end of lactation from: 4-6 (Group 1); 12-14 (Group 2); or 37-40 weeks gestation (Group 3).</td>
<td>75</td>
<td>Brunet-Lezine developmental quotient of children at 18 months was: 101.8 in Group 1 vs 92.2 in Group 2 (p&lt;0.05) or 87.5 in Group 3 (p&lt;0.001).</td>
</tr>
</tbody>
</table>
The consequences of milder types of iodine deficiency (i.e. MUIC 100-150 µg/L) in pregnancy have yet to be elucidated. In countries, such as Australia and New Zealand, which have seen the re-emergence of mild iodine deficiency in the last two decades, there appears to be no obvious signs of impaired neurodevelopment over this period with children meeting the usual developmental milestones at appropriate times. It is possible that in mild iodine deficiency adaptive mechanisms conserve iodine in the mother, such that the mother can supply the infant with sufficient thyroid hormones for normal brain development; the parasitic nature of the fetus in pregnancy is well-known. To date, there are no published studies examining the effect of iodine supplementation in mildly iodine deficient pregnant women on neurodevelopment in children to date, however, by 2015 the results of several ongoing randomised, placebo-controlled, intervention trials being conducted in Thailand, India [27], Australia and New Zealand should be available. Conducting such trials will become increasingly difficult in the coming years, as more populations become iodine sufficient around the world.

6. Conclusion

Severe iodine deficiency during pregnancy is a known cause of cretinism and mental retardation. At present, there are limited data on the cognitive deficits of children born to mothers who are moderately iodine deficient in pregnancy. There is a need for well designed clinical trials investigating whether routine iodine supplementation of pregnant women living in regions of mild iodine deficiency improves neurodevelopment in children.

References


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