

## Issue 325

### In a nutshell

Iodine is required for thyroid hormone production, which is crucial to brain development. Iodine deficiency is widespread throughout the world, and mild deficiency is surprisingly common in developed countries.

There is some good evidence that even milder deficiencies are associated with cognitive deficit. Public health policy is important (e.g. iodine fortification of salt), but also clinicians should be aware of individual iodine status, especially in pregnant women and children.

## Iodine and the brain

Arbor Clinical Nutrition Updates 2010 (Nov);325:1-4 ISSN 1446-5450

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## NUTRITION RESEARCH REVIEW

### Study 1: Iodine in pregnant women

A new Australian study looked at the iodine status of healthy pregnant women.

**Subjects and method:** Cross-sectional observational study on 139 pregnant women (from each trimester) who were attending public hospital antenatal clinic. Urine iodine concentration (UIC) was measured and they completed a questionnaire on food sources of iodine.

**Results:** The median UIC was 87.5 µg/L, 14.5% of participants had UIC ≥150 µg/L (this is the WHO standard for normal iodine for pregnancy, with ≥100 µg/L being the standard for non-pregnant), 45.5% were between 50-99-µg/L (mild deficiency) and 15% were <50 µg/L (severe deficiency). Only a half of the women could identify good food sources of iodine, and only 11% had changed their diet during pregnancy to increase iodine intake.

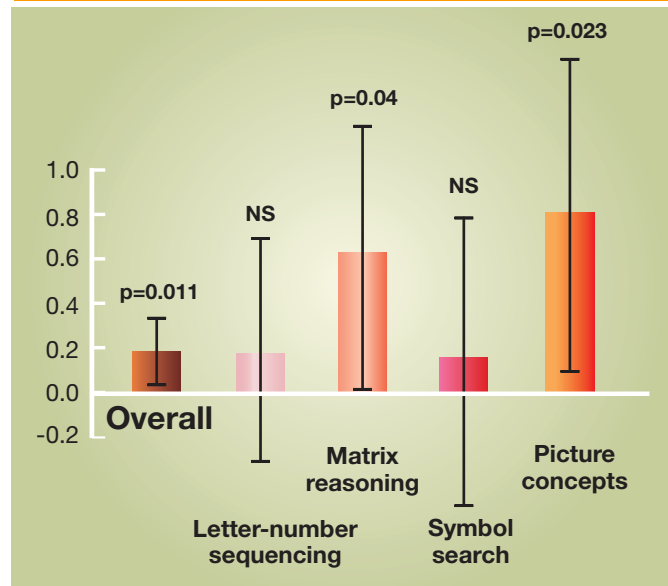
*Ref. Charlton KE. et al. Suboptimal iodine status of Australian pregnant women reflects poor knowledge and practices related to iodine nutrition. Nutrition. 2010 Oct;26(10):963-8.*

### Study 2: The impact of iodine in pregnancy

A recent study from Spain considered the impact on children of iodine supplementation during pregnancy.

**Subjects and method:** Observational study on the children of 133 women given iodine (300 µg/day) during pregnancy (starting during the first trimester), compared with children from 61 women who did not receive it.

**Graph 1: Cognitive effect of iodine:** Age-adjusted (Study 3) WISC test scores, treatment effect (SD)



**Results:** When tested at somewhere between 3 and 18 months of age, the children of supplemented mothers had higher psychomotor and behaviour rating scores than the control children.

*Ref. Velasco I. et al. Effect of iodine prophylaxis during pregnancy on neurocognitive development of children during the first two years of life. J Clin Endocrinol Metab. 2009 Sep;94(9):3234-41.*

### Study 3: Iodine supplement for normal children

A recent clinical trial in New Zealand trial investigated what happens when healthy children are given iodine.

**Subjects and method:** Randomised, controlled trial in 184 10-13 year olds, none of whom had any diagnosed thyroid problem or any other sign of iodine deficiency. They were randomised to receive either placebo or iodine (150 µg/day) for 28 weeks.

**Results:** The baseline UIC values showed that this was a mildly iodine deficient population (median UIC=66 µg/L, interquartile range 45-88; 87% had

UIC <100 µg/L, 32% were <50 µg/L, median serum thyroglobulin concentration 16.4 lg/L). Compared to placebo, iodine supplemented children had significant improvement in overall cognitive and two sub-scale scores - see Graph 1 (preceding page).

*Ref. Gordon RC. et al. Iodine supplementation improves cognition in mildly iodine-deficient children. Am J Clin Nutr. 2009 Nov;90(5):1264-71.*

## COMMENTARY

The requirement of having adequate iodine for normal brain development during foetal life and early childhood is probably the single most clear cut relationship between any one nutrient and cognition.

Around 70-80% of the body's iodine is found in the thyroid gland, where it is converted by a series of synthetic steps into the bioactive forms of thyroxine (T4) and triiodothyronin (T3). It is these thyroid hormones, required throughout the body for normal cell metabolism, that cause brain deficits in cases of iodine deficiency. Thyroid hormones appear to have a role in various processes such as neurogenesis, neuronal migration, axon and dendrite formation, myelination, synaptogenesis and neurotransmission <sup>1</sup>.

When the thyroid gland has insufficient iodine for its needs, it responds by reducing the synthesis of T4 in favour of T3, since the latter requires less iodine in its manufacture. This occurs even before levels of TSH begin to rise. This relative lack of T4, even in the face of 'normal' TSH levels, can cause neurocognitive deficits, particularly in the developing foetus during the time it is entirely dependent on maternal T4, which is the first 24 weeks or so of pregnancy <sup>1-4</sup>.

T4 exerts its effect in the foetal brain by being converted locally there to T3 and then binding to T3 brain receptors. These in turn regulate the expression of specific genes in different brain regions following a precise development schedule <sup>5</sup>. Since these nuclear T3 receptors are present in the human brain from ten weeks gestational age, and yet the onset of foetal thyroid function is not until 24 weeks, the dependency of the foetus on maternal T4 during this time is obvious. Indeed maternal T4 still makes up between 20-50% of cord T4 <sup>2</sup>.

All in all, this means that pregnancy brings about an increase in maternal iodine requirement of around 50% over non-pregnant levels and that mild iodine deficiency might not be picked up by TSH assay. Thereafter the need for adequate thyroid hormone continues postnatally and for some time, given how much the brain must grow after birth (it is only one third of its adult size at birth!) <sup>1-4</sup>.

Animal studies have shown that the impact of thyroid hormone deficiency depends on the timing. During the first and second trimesters the most obvious adverse



**Iodised salt consumption is a mainstay of public health programs to prevent iodine deficiency**

effects are on visual attention and processing and fine motor skills, during the second and third trimesters on gross motor skills, memory and motor function, postnatally in language and verbal development, attention and memory skills <sup>1</sup>. More severe lack results in lower brain weight, but greater density because of failed arborisation of axons and dendrites and retarded myelination. This occurs in the cerebrum, but especially in the cerebellum <sup>2, 4</sup>.

In humans, iodine deficiency reflects in many of these domains. The most severe deficiency state results in 'cretinism' and may include mental retardation, deaf-mutism and spasticity, not easily reversible even if iodine status is later repaired. In less severe deficiencies, cognitive deficits may be seen from the second year of life and include subtle neurological changes, impaired psychomotor, learning and academic performance, and in IQ <sup>1, 2, 4</sup>.

Two meta-analyses have attempted to estimate the size of this IQ deficit in iodine deficient vs replete children. Although in both cases the methodology of the studies was a rather imperfect base from which to make an estimate of any precision, in the first meta-analysis the difference reported was 13.5 IQ points <sup>6</sup>. In the second meta-analysis, the reviewers collated thirty seven studies from China on 12,291 children. In the majority of these studies, comparisons had been based on the area where the child lived (e.g. iodine replete vs deficient, supplemented vs non-supplemented), rather than comparing the iodine status of individual subjects. The intelligence differences reported were in the region of between 5 and 12 IQ points, with the upper end of the scale being seen in those exposed to high risk of severe iodine deficiency <sup>7</sup>.

In adults, iodine deficiency is likely to manifest as hypothyroidism and in the elderly, paradoxically, sub-clinical hyperthyroidism, both of which can present with mental sluggishness <sup>1-3</sup>.

What is most worrying from a clinical perspective is the evidence that even moderate iodine and thus thyroid hormone deficiency during the vulnerable period of pregnancy and early childhood can result in cognitive deficit<sup>1, 8-10</sup>. Such modest deficiency may not even be clinically apparent, and hence go uncorrected.

For example, in an American study, researchers tested the 7-9 year old children of women whose only suggestion of what was in essence subclinical and undiagnosed hypothyroidism during that child's pregnancy was that blood collected from the mother at the time for the study (but not used clinically at that time) showed a free T4 below the 10th percentile at 12 week gestation. These offspring had an IQ deficit of 4 points compared with children of mothers with normal T4 during the pregnancy<sup>11</sup>. A similar result was seen at 10 months post-partum follow up in Dutch children<sup>12</sup>. This is worrying because moderate iodine deficiency is by no means uncommon, even in developed countries.

The iodine content of foods varies with geographical region, depending on the content of the soils in those regions, but there are many regions where it is marginal. Moreover, although the absorption of iodine in itself is high, many plant foods contain goitrogens that reduce the bioavailability. The most reliable source is seafood, since marine plants and animals concentrate iodine from seawater<sup>13, 14</sup>.

Globally, iodine deficiency remains a huge public health problem, with something like 2 billion people estimated by some experts to have inadequate iodine nutrition<sup>1, 13</sup>. Iodine deficiency has been called the single greatest preventable cause of impaired mental development in children<sup>9, 15-17</sup>.

In developed Western countries, such as Australia (where new Study 1 took place), the story is more nuanced. Like many countries, Australia had a long history of iodised salt which, although not compulsory, led to something of a sense of complacency about the level of iodine insufficiency in the population. Yet over the last decade, studies there and in other similarly ostensibly well-nourished countries have shown that significant proportions of the population have sub-optimal iodine status, as judged for example by TSH readings, thyroid size or urine iodine excretion<sup>3</sup>. New Study 1 complements the findings of a national iodine nutrition survey in the same country, in which between 48% and 73% (depending on location) of 1,709 children (average age 9 years) had mild iodine deficiency, and 4-18% were moderate to severely deficient<sup>18</sup>.

New Study 1 found that, amongst Australian pregnant women, 46% had mild and 15% severe deficiency. The 'relapse' in the prevalence of iodine deficiency in that country over the last 10 years is believed to be due to a combination of the success of public health messages about the need to reduce voluntary salt intake, less use of iodised salt by food manufacturers

and switch from iodine to chlorine based cleansers in the dairy industry<sup>14, 17</sup>. The wider public health implication for all countries may be that voluntary fortification is probably going to be insufficient as a policy, and indeed Australia has recently introduced a mandatory fortification program for bread.

A number of trials of iodine supplementation as primary prevention against cognitive damage have been carried out in high risk pregnant women and children in developing world countries, such as New Guinea, Benin, Malawi and Bangladesh. Results have been mixed, some showing improved cognitive outcomes, others not<sup>1, 19-31</sup>. In Western countries, for example in Europe, similar trials of supplementing pregnant women with iodine have been done, but have tended to be judged by measuring thyroid or TSH response, rather than cognitive outcome<sup>13, 17, 32</sup>. As discussed above, this may be misleading because what is happening to T3 supply within the brain is not always obvious by looking at thyroid measures on the body side of the blood-brain barrier!

New Study 2 is therefore valuable because it is one of the few studies on Western pregnant women that has reported on cognitive outcome, even though it was far from being a randomised controlled trial. In another Spanish study, cognitive testing was conducted at 18 months of age in children from pregnancies in one of three categories: where the mothers were of normal T4 status and supplemented from the 4-6 weeks pregnancy, or successfully treated for mild hypothyroxinaemia with iodine supplementation some time within the first trimester, or T4 deficient at delivery but supplemented to the end of lactation. The children of the first group had better developmental and socialization quotients, gross and fine motor coordination than the other two groups, and were the only group to have no delayed neurobehavioural outcomes<sup>33</sup>.

New Study 3 is a far more powerful design to address the challenge of undetected mild iodine deficiency in children. Although New Zealand is a country known to have some problem with iodine in the food supply, it is nevertheless a prosperous, developed Western nation. The baseline status of these children was not so different to those reported in new Study 1.

The outcome of this Study is a sobering reminder that there is an undiagnosed and untreated level of iodine deficiency sufficient to affect cognitive performance, existing even within healthy Western children. Routine neonatal screening for congenital hypothyroidism will certainly not pick up this level of iodine deficiency.

How this plays out in a given country depends very much on their public health policy with regard to fortification, and each of our readers must assess their own local situation. But even in countries with compulsory iodine fortification, health professionals should remain vigilant in those who do not consume much of the fortified foods, or seafood, particularly when pregnant. There is much at stake!

#### References:

1. Melse-Boonstra A. et al. Iodine deficiency in pregnancy, infancy and childhood and its consequences for brain development. *Best Pract Res Clin Endocrinol Metab.* 2010 Feb;24(1):29-38.
2. DeLange F. et al. The iodine deficiency disorders. Ch.20 Supporting documentation for medical course, University of Fiji, 2001, on web at: [http://application.fnu.ac.fj/classshare/Medical\\_Science\\_Resources/MBBS/MBBS1-3/PBL/Endocrine/Thyroid/Chapter%2020-Iodine%20Deficiency%20Disorders.pdf](http://application.fnu.ac.fj/classshare/Medical_Science_Resources/MBBS/MBBS1-3/PBL/Endocrine/Thyroid/Chapter%2020-Iodine%20Deficiency%20Disorders.pdf)
3. Gallego G. et al. Iodine deficiency in Australia: is iodine supplementation for pregnant and lactating women warranted? *Med J Aust.* 2010 Apr 19;192(8):461-3.
4. Lazarus J. Iodine and brain function. Ch 15 In: Kanarek RB, Lieberman H, Prasad C. (eds). *Nutritional Neuroscience.* CRC Press, Boca Raton, FL, 2005.
5. Bernal J. Thyroid hormones and brain development. *Vitam Horm.* 2005;71:95-122.
6. Bleichrodt N. et al. Measuring intelligence and learning potential in iodine-deficient and non-iodine deficient populations. In: Stanbury JB, ed. *The damaged brain of iodine deficiency.* New York: Cognizant Communication, 1994:37-42.
7. Qian M. et al. The effects of iodine on intelligence in children: a meta-analysis of studies conducted in China. *Asia Pac J Clin Nutr.* 2005;14(1):32-42.
8. Kooistra L. et al. Neonatal effects of maternal hypothyroxinemia during early pregnancy. *Pediatrics.* 2006 Jan;117(1):161-7.
9. Zimmermann MB. Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review. *Am J Clin Nutr.* 2009 Feb;89(2):668S-72S.
10. Choudhury N. et al. Subclinical prenatal iodine deficiency negatively affects infant development in Northern China. *J Nutr.* 2003 Oct;133(10):3162-5.
11. Haddow JE. et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med.* 1999 Aug 19;341(8):549-55.
12. Pop VJ. et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clin Endocrinol (Oxf).* 1999 Feb;50(2):149-55.
13. Zimmermann MB. Symposium on 'Geographical and geological influences on nutrition': Iodine deficiency in industrialised countries. *Proc Nutr Soc.* 2010 Feb;69(1):133-43.
14. Cunnane SC. Origins and evolution of the Western diet: implications of iodine and seafood intakes for the human brain. *Am J Clin Nutr.* 2005 Aug;82(2):483.
15. Hetzel BS. Iodine and neuropsychological development. *J Nutr.* 2000 Feb;130(2S Suppl):493S-495S.
16. Li M. et al. Re-emergence of iodine deficiency in Australia. *Asia Pac J Clin Nutr.* 2001;10(3):200-3.
17. Pearce EN. What do we know about iodine supplementation in pregnancy? *J Clin Endocrinol Metab.* 2009 Sep;94(9):3188-90.
18. Li M. et al. Are Australian children iodine deficient? Results of the Australian National Iodine Nutrition Study. *Med J Aust.* 2006 Feb 20;184(4):165-9.
19. Connolly KJ. et al. Foetal iodine deficiency and motor performance during childhood. *Lancet.* 1979 Dec 1;2(8153):1149-51.
20. Pharoah PO. et al. Effects of maternal iodine supplementation during pregnancy. *Arch Dis Child.* 1991 Jan;66(1):145-7.
21. Hess SY. et al. Treatment of iron deficiency in goitrous children improves the efficacy of iodized salt in Côte d'Ivoire. *Am J Clin Nutr.* 2002 Apr;75(4):743-8.
22. van Stuijvenberg ME. et al. Effect of iron-, iodine-, and beta-carotene-fortified biscuits on the micronutrient status of primary school children: a randomized controlled trial. *Am J Clin Nutr.* 1999 Mar;69(3):497-503.
23. Huda SN. et al. Cognitive and motor functions of iodine-deficient but euthyroid children in Bangladesh do not benefit from iodized poppy seed oil (Lipiodol). *J Nutr.* 2001 Jan;131(1):72-7.
24. Zimmermann MB. et al. Iodine supplementation improves cognition in iodine-deficient schoolchildren in Albania: a randomized, controlled, double-blind study. *Am J Clin Nutr.* 2006 Jan;83(1):108-14.
25. Manger MS. et al. A micronutrient-fortified seasoning powder reduces morbidity and improves short-term cognitive function, but has no effect on anthropometric measures in primary school children in northeast Thailand: a randomized controlled trial. *Am J Clin Nutr.* 2008 Jun;87(6):1715-22.
26. Bautista A. et al. The effects of oral iodized oil on intelligence, thyroid status, and somatic growth in school-age children from an area of endemic goiter. *Am J Clin Nutr.* 1982 Jan;35(1):127-34.
27. Wang YY. et al. Improvement in hearing among otherwise normal schoolchildren in iodine-deficient areas of Guizhou, China, following use of iodized salt. *Lancet.* 1985 Sep 7;2(8454):518-20.
28. Shrestha RM. The effect of iodine and iron supplementation on physical, psychomotor and mental development in primary school children in Malawi. PhD thesis. Division of Human Nutrition, Wageningen University: the Netherlands; 1994.
29. Isa ZM. et al. Effect of iodized oil supplementation on thyroid hormone levels and mental performance among Orang asli schoolchildren and pregnant mothers in an endemic goitre area of peninsular Malaysia. *Asia Pac J Clin Nutr.* 2000; 9(4): 274-281.
30. van den Briel T. et al. Improved iodine status is associated with improved mental performance of schoolchildren in Benin. *Am J Clin Nutr.* 2000 Nov;72(5):1179-85.
31. Pharoah PO. et al. A controlled trial of iodinated oil for the prevention of endemic cretinism: a long-term follow-up. *Int J Epidemiol.* 1987 Mar;16(1):68-73.
32. Zimmermann MB. Iodine deficiency. *Endocr Rev.* 2009 Jun;30(4):376-408.
33. Berbel P. et al. Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. *Thyroid.* 2009 May;19(5):511-9.

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