THYROID FUNCTION

Thyroid hormones, iodine and the brain—an important concern

Peter Laurberg

Exposure of the fetus to low levels of thyroid hormones for extended periods during pregnancy can lead to irreversible brain damage and potential delays in neurological and behavioral development. What are the exact mechanisms behind this abnormality, and can prompt initiation of maternal iodine supplementation prevent this adverse effect?

Thyroid hormones are important regulators of brain development, and exposure to insufficient levels of these hormones for more than short periods of time during fetal development can lead to irreversible brain damage. The only source of thyroid hormones available to the fetus during the first trimester of pregnancy is derived from the mother; however, fetal production of thyroid hormones becomes increasingly important during the second half of pregnancy. Thyroid function should, therefore, be optimal in both pregnant women and their offspring if adverse effects on brain development are to be avoided. Investigators from Spain have made important contributions to the characterization of fetal abnormalities caused by maternal thyroid insufficiency in animals.[1] This research has now been extended to a clinical study of neurological and behavioral development in young children whose mothers lived in an area where mild iodine deficiency was prevalent.[2] Berbel and colleagues conclude that even a short delay of 6–10 weeks before initiation of iodine supplementation might lead to delayed brain development in the offspring of women with low free T_4 levels during early pregnancy.

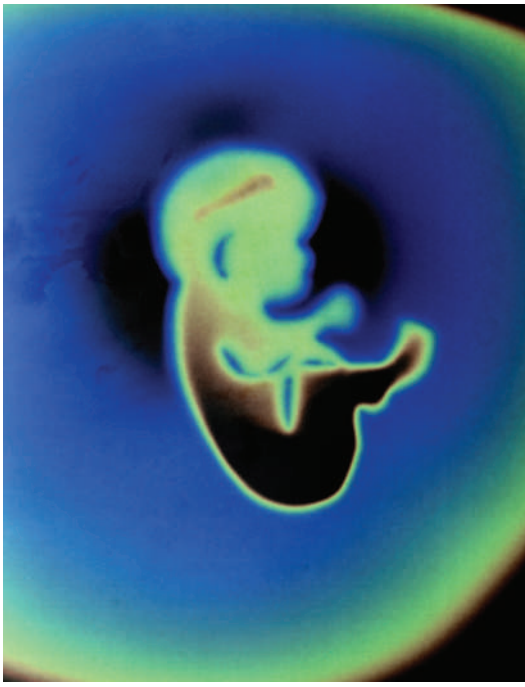
Berbel *et al.* enrolled 345 pregnant women living in the mildly iodine-deficient Marina Baixa region of Spain. The investigators identified three subgroups of women: those with free T_4 levels >20th percentile in early pregnancy (weeks 4–6) and at term (group 1); those with free T_4 levels ≤10th percentile at weeks 12–14 of gestation but >20th percentile at term (group 2); and those with free T_4 levels ≤10th percentile at term (group 3). Daily iodine supplementation was started in weeks 4–6 (group 1), weeks 12–14 (group 2) or at term (group 3); all women received iodine supplements during lactation. Neurological and behavioral development was investigated in a total of 44 children at 18 months of age. Whereas none of the children whose mothers were assigned to group 1 showed delayed neurological or behavioral development, such delays (predominantly in motor and social skills) were observed in 25.0% of children of group 2 mothers and 36.8% of children of group 3 mothers.

The study of Berbel *et al.* is just one of many that have raised concerns about impaired thyroid function in pregnant women and subsequent brain development in the child. These studies fall into three key categories, each of which represents a different area of concern: thyroid insufficiency caused by low iodine intake (of the mother and the child); primary maternal thyroid insufficiency with a higher than normal serum TSH concentration; and isolated low free T_4 levels in the mother.

Severe iodine deficiency—defined as a median, population-based urinary iodine concentration <20 μg/l—is associated with impairments in brain development that range from frank cretinism with multiple defects of the central nervous system to a lower than anticipated intelligence quotient. Some studies have indicated that moderate iodine deficiency (median urinary iodine concentrations 20–49 μg/l) might also increase the risk of impaired brain development in some individuals.[3,4] However, whether the mothers of affected children had below-average iodine intake is unclear, as is the issue of whether even a mildly low iodine intake (≥50 μg/l but <100 μg/l) is sufficient to hamper development in some children. Furthermore, the question of whether the children with iodine deficiency had been exposed to additional nutritional deficiencies or other environmental hazards is unresolved.

Our current understanding suggests that the effect of low iodine intake on brain development is mediated by a combined impairment of maternal and fetal thyroid function, caused by inadequate levels of substrates for thyroid-hormone synthesis. Production of thyroid hormones increases during pregnancy; in consequence, maternal need for iodine is also increased. The WHO recommends, therefore, that pregnant and lactating women should increase their daily iodine intake to protect thyroid function and fetal development.[5] The median urinary iodine concentration currently recommended by the WHO is 150–249 μg/l for pregnant women, a level considerably greater than that recommended for nonpregnant adults (100–199 μg/l).

Pregnant women whose serum TSH levels are elevated give cause for concern, as such increases indicate primary maternal thyroid insufficiency. If iodine intake is adequate, the most likely causes of elevated maternal TSH levels are undiagnosed autoimmune thyroiditis and inadequately treated, previously diagnosed thyroid dysfunction. Several studies have found associations that suggest elevated maternal TSH concentrations might have deleterious effects on various aspects of pregnancy outcome,[6,7] although the complications observed tend to differ somewhat between studies. These findings have led to discussion about the feasibility of TSH screening for all women in early pregnancy. The current recommendation is active case-finding, as the documentation requirements for screening are not yet



Practice points

- WHO guidelines on iodine nutrition should be followed
- Active case finding of thyroid disorders should be performed in early pregnancy
- Further research is needed on the causes and potential consequences of low free T_4 levels in early pregnancy

fulfilled. Results of prospective studies are, therefore, keenly awaited.

An unusual subgroup of women is those with isolated low serum free T_4 levels in early pregnancy. Investigators in The Netherlands[8] found that a mother with a first-trimester free T_4 concentration $\leq 10^{th}$ percentile (in the group of mothers studied) was at greater than average risk of having a child with some degree of retarded brain development. By contrast, no association between fetal brain development and maternal serum TSH concentration in the first trimester or free T_4 level in late pregnancy was detected, and these mothers had no indication of iodine deficiency.

The reason for a lower than average free T_4 level in the first trimester of pregnancy in some women has not been clarified—except that a portion of any group will always have levels at the low end of the normal distribution curve. One possibility is that low free T_4 levels are a sign of suboptimal placental function during early pregnancy, which leads to reduced stimulation of the thyroid gland by human chorionic gonadotropin. Developmental delays might, therefore, be a direct consequence of the low serum free T_4 levels or represent a covariant effect of early placental insufficiency. A more speculative suggestion is that the low free T_4 levels might be an artifact of measurement caused by assay interference that somehow correlates with delayed brain development. In pregnant women, the results obtained with automated, nonseparation assays of free T_4 correlate poorly with those obtained by reference methods, in which free T_4 has been isolated by ultrafiltration or equilibrium dialysis before analysis.[9]

Berbel and co-workers observed low free T_4 levels (with normal TSH concentrations) in some of the pregnant women enrolled in their study, and assumed that the low free T_4 value was caused by iodine deficiency. However, no evidence in support of this hypothesis was presented, except for the fact that the women lived in an area where mild iodine deficiency was prevalent. The presence of iodine deficiency can be difficult to evaluate in pregnancy.[10] In general, no easy methods exist to evaluate iodine deficiency in individuals, only in groups. Furthermore, changes occur in both total and free serum thyroid hormone concentrations during pregnancy that are not caused by iodine deficiency. Moreover, the subgroups of women and children studied by Berbel *et al.* were highly selected, which might have introduced some bias.

Several studies now indicate that a child may exhibit delayed neurological and behavioral development in early life if the mother had mildly low free T_4 levels in early pregnancy. The precise cause of such reductions in free T_4 levels has not been clarified, and whether some sort of preventative approach might be feasible is unclear. Berbel and colleagues suggest that low free T_4 levels during pregnancy might be caused by iodine deficiency in some women, and that affected women should be given iodine supplements as early as possible to counteract adverse effects on fetal brain development. Although limitations in the study design do not allow strong conclusions to be drawn, the findings presented by Berbel *et al.* add to already increasing concerns about the association between adequate iodine supply, thyroid function in pregnancy, and brain development in the child.

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Competing interests
The author declares no competing interests.

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THERAPY

A new nonsurgical therapy option for benign thyroid nodules?

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Despite the increasing implementation of iodization programs, benign nodular thyroid disease will remain a prevalent therapeutic concern for decades. Recent research suggests that nonsurgical therapy, including radioactive iodine, radiofrequency thermal ablation and percutaneous laser ablation, might have a role in the treatment of symptomatic patients.

Simple nodular thyroid disease—benign uninodular and multinodular goiter, in a euthyroid individual, that does not result from an autoimmune process—is common. An estimated 5–10% of the adult population will eventually need therapy for simple