Keep an Eye on Iodine and the Thyroid and Save the Brain

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Thyroid hormones are indispensable developmental factors and a lack of adequate amounts of thyroid hormone during brain development may lead to irreversible brain damage [1]. Thus, it is vital that neonates diagnosed with hypothyroidism are treated fast and adequately to become euthyroid. In this issue of *Hormone Research in Paediatrics*, Kurtoglu and colleagues from Kayseri, Turkey, report an interesting study where an iodine supplement was added to the obligatory levothyroxine replacement therapy of neonates diagnosed by screening to suffer from hypothyroidism [2].

A lack of thyroid hormone for proper brain development may have several main causes: (1) maternal thyroid insufficiency, because the thyroid hormones involved in steering the development in early pregnancy are entirely of maternal origin, and those involved in late pregnancy are partly of maternal (and partly of fetal) origin. The typical cause is autoimmune impairment of the thyroid in the mother, and it is much discussed if all pregnant women should be screened in early pregnancy for thyroid dysfunction [3]. (2) Fetal/neonatal/infant thyroid insufficiency is most often caused by developmental defects such as thyroid aplasia/hypoplasia/ectopia or abnormalities in processes involved in thyroid hormone production [4]. Screening for neonatal hypothyroidism is now part of public healthcare in many countries, but still only a minority of the world's newborns are screened [4]. (3) Insufficient thyroid hormone production in both the mother and the fetus/infant is typically caused by an insufficient

iodine content of the mother's diet. Iodine readily passes the placenta [5], and the mother's dietary iodine intake should cover the needs of both the maternal and the fetal thyroid hormone production. Compared with the non-pregnant state, the thyroid hormone production is up to 50% higher from early pregnancy due to a high degradation rate of T₄ in the placenta/uterus unit and various other mechanisms [3]. Thus, iodine requirements are substantially increased in pregnancy [1]. During breastfeeding, around 40% of iodine in the mother's diet are transferred to the infant via breast milk [6, 7], and the mother's iodine intake should be relatively high to cover both her own needs and the iodine transfer via breast milk [1]. Smoking and other sources of thiocyanate diminish iodine transport into breast milk [8], and mothers who smoke or who are exposed to other inhibitors of the mammary gland iodine transport should have an even higher iodine intake.

A few months' delay in the diagnosis and therapy of congenital hypothyroidism involves a high risk of some degree of permanent intellectual impairment of the child. As a consequence, a neonatal screening program for hypothyroidism was initiated in Turkey in 2006 [2]. Moreover, considerable parts of the Turkish population had previously been affected by iodine insufficiency, and a program of salt iodisation was introduced in the late 1990s [9].

Even if salt iodisation has in general increased iodine intake in the Turkish population [9], areas of low iodine

intake are still to be found [10]. Kurtoğlu et al. [2] hypothesised that some of the neonates diagnosed with hypothyroidism by screening might have developed it because of low maternal iodine intake, and they performed a randomised study comparing therapy of hypothyroid neonates with levothyroxine alone versus levothyroxine plus iodine. The neonates included had high serum TSH, low fT_4 and a spot urine iodine concentration $<100 \mu\text{g/l}$. Many details on the selection for the study are lacking, but apparently neonates with thyroid aplasia/hypoplasia/ectopia were excluded, because a normal or enlarged thyroid gland evaluated by ultrasonography was present in all the children, and they all had high serum thyroglobulin levels at inclusion. The children were studied before therapy and again after 1 and 3 months. No differences between the treatment groups were observed in the rates of serum TSH and fT_4 normalisation, or in thyroid size and serum thyroglobulin.

The results of the study illustrate the effectiveness of the current standard therapy of neonatal hypothyroidism with levothyroxine. On the other hand, iodine supplements to the neonates had no effect.

Are the results of this study an indication that adequate iodine intake during pregnancy and lactation is of little importance for the thyroid function of the offspring? This is certainly not a conclusion to be drawn from the study.

Even if Kurtoğlu et al. [2] are to be congratulated for their prospective randomised study, there are some limitations to the study as was also pointed out by the authors.

Apparently, the study was not blinded to the mothers and judging by the measured iodine concentrations in breast milk and infant urine, the mothers in the levothyroxine only group tended to increase their iodine intake to compensate the risk they may have feared to their children. An important detail to consider when discussing iodine intake and levothyroxine therapy is that iodine constitutes 65% of levothyroxine by weight, and levothyroxine replacement therapy is also to some degree an iodine supplement.

Another limitation is the method used by Kurtoğlu et al. [2] to diagnose iodine deficiency as the cause for hypothyroidism in the neonates (a single spot urine iodine concentration $<100 \mu\text{g/l}$). Urinary iodine concentrations show large intraindividual variation, and in general iodine deficiency in an individual cannot be diagnosed from a single spot urine concentration [11]. Even if the neonates had low iodine intake, iodine deficiency would normally have to be much more severe than in this study to result in the high serum TSH levels recorded in these neonates [12], and if iodine deficiency was the only cause of the impaired neonatal thyroid function, the condition would be curable with simple iodine intake normalisation alone.

In conclusion, brain development is critically dependent on thyroid hormones and considerable effort should be devoted to keep pregnant women and their children euthyroid. This is done by adequate iodine nutrition and by early detection and therapy of thyroid function abnormalities in the mother and her fetus/child.

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