Thoughts about the ‘Antenatal Thyroid Screening and Childhood Cognitive Function’ Study

Roberto Negro

Division of Endocrinology, ‘V. Fazzi’ Hospital, Lecce, Italy

Dear Sir,

The results of the long awaited Antenatal Thyroid Screening and Childhood Cognitive Function study have finally been published in the *New England Journal of Medicine* after a preliminary presentation of findings at the International Thyroid Congress in Paris in 2010 [1].

The aim of the study was to evaluate the impact of levothyroxine (LT4) treatment on the intelligence quotient (IQ) of 3-year-old children born from mothers with mild thyroid impairment. This prospective, randomized, multicenter study involved almost 22,000 patients who were recruited within the first 16 weeks of gestation. Patients were divided into a ‘screening’ group and a ‘control’ group. In the screening group, patients were tested for TSH and free T4 (FT4) at the time of recruitment, and women with a TSH >97.5 percentile and/or FT4 <2.5 percentile were treated with levothyroxine at an initial dosage of 150 µg/day. Patients in the control group had their blood drawn at the time of recruitment, but their thyroid function test results were not known until after delivery. Thyroid dysfunction was found in 4.6% of the screening group and in 5% of the control group. There were no differences in patient characteristics between the two groups (age, smoking, weight, education, preterm birth). LT4 treatment was initiated at 13 weeks’ gestation in the screening

group (median). The standardized IQ of children in the control group was 100 points (404 children, 73.3% of the children of the women who tested positive), whereas the IQ of children in the screening group (390 children, 78.2% of the children of the women who tested positive) was 99.2 points ($p = 0.40$). The proportion of patients with an IQ <85 points was 12.1% in the screening group versus 14.1% in the control group ($p = 0.39$). A post-hoc analysis revealed no difference when controls were compared with different patient subgroups, namely women with elevated TSH only, low FT4 only, or women who started treatment either before or after 14 weeks’ gestation.

In conclusion, the Antenatal Thyroid Screening and Childhood Cognitive Function study demonstrated that in pregnant women with mild thyroid impairment, treatment with LT4 initiated at a median of 13 weeks’ gestation did not improve the IQ of their offspring when tested at age 3 years.

This study involved 10 centers in the United Kingdom and 1 center in Italy (Turin), and has the merit of being one of the very few prospective studies of intervention for thyroid disease during pregnancy. There is an extensive and ongoing debate regarding the pros and cons of universal screening for thyroid dysfunction during

pregnancy. At the center of the debate has been the limited data on the utility, or lack thereof, for treating subclinical hypothyroidism during pregnancy (as there is unanimous consensus about treating overt hypothyroidism) [2]. As the study results did not demonstrate a benefit for LT4 treatment during pregnancy, it provides data against the benefit of universal screening.

As with all studies, this one has its debatable points, which are discussed below.

Suitability of the Control Group

The ideal control group for this study, which is lacking, would have been the IQ results of the offspring of euthyroid mothers. This would have permitted a comparison of the IQ of children born from hypothyroid untreated mothers with the IQ of children born from euthyroid mothers. This initial comparison would identify if there is an IQ difference between the offspring of women with mild thyroid impairment versus euthyroid women. If a significant difference in IQ was found, the intervention component of the study would have demonstrated whether LT4 intervention is beneficial in improving IQ. Consequently, the lack of effect in the study by Lazarus et al. [1] may simply be due to a lack of disease.

Statistical Power in Groups and Subgroups of Patients

The number of patients recruited (approx. 22,000) and expected to complete the study (about 400 for each group) were based on a publication by Haddow et al. [3] in which women with a high TSH level were three times more likely to have children with an IQ that was ≤ 85 points as compared to women with a normal TSH during pregnancy. However, whereas in the study by Haddow et al. [3], patients were considered positive solely on the basis of an elevated TSH, in the study by Lazarus et al. [1], patients were considered positive either with an elevated TSH and normal FT4 or with a normal TSH and decreased FT4. As recruitment in the Lazarus study only included approximately 200 patients in the screening group and 200 patients in the control group with an elevated TSH, the study was underpowered to detect a difference between the groups. If thyroxine exerts a central role in fetal brain development, especially in the first trimester, putting together patients with high TSH (and normal FT4) and patients with low FT4 (and normal TSH) may have added a confounder to the final results [4].

Date of Commencement of LT4 at 13 Weeks' Gestation

Initiation of LT4 intervention began at 13 weeks' gestation. As the fetal thyroid begins to secrete thyroid hormone at the beginning of the second trimester, it is feasible that the lack of effect was secondary to the fact that LT4 therapy was begun too late in gestation. It would be important to know if a beneficial effect would have been derived if treatment was started earlier. Of note, I would like to bring to the

reader's attention a recently published paper by Momotani et al. [5]. In this manuscript, published in the *Journal of Clinical Endocrinology Metabolism*, the author reported 5 cases of pregnant women with severe hypothyroidism diagnosed and treated with LT4 within 12 weeks of gestation. The TSH at diagnosis ranged from 40.4 to 657.8 mIU/l, and the IQ of the offspring measured at an age between 2 and 11 years were all normal. Based on the study by Momotani et al. [5], in conjunction with the known negative impact of untreated overt hypothyroidism on the IQ of the offspring, it appears that initiation of LT4 treatment within the first trimester is able to prevent decreased IQ in the offspring. In this view, if in the patients of Lazarus et al. [1] thyroid dysfunction would have adversely affected offspring IQ, it is reasonable that starting treatment at 13 weeks' gestation was effective anyway.

The Relatively Mild Degree of Hypothyroidism

The median TSH of participants from the United Kingdom was 3.8 mIU/l (interquartile range: 1.5–4.7), and from Italy was 3.1 mIU/l (interquartile range: 1.3–4.0). This degree of hypothyroidism was probably too mild to result in a significant difference between treated and untreated patients. In comparison, the observational study by Haddow et al. [3], which reported a difference of IQ in 7- to 9-year-old children, had a mean TSH which was fourfold higher than in the study by Lazarus et al. [1]. It is also possible that the IQ measurement is not a sensitive enough index to identify deleterious effects of such a subtle dysfunction. It is noteworthy, that Lazarus et al. [1] highlighted that the degree of

subclinical hypothyroidism/hypothyroxinemia in their study may be associated with specific defects (language, orientation, memory, attention) more than a reduction in IQ.

The Accuracy of FT4 Immunoassay in Pregnancy

Current uncertainty about FT4 estimates in pregnancy has led some investigators to question the reliability of FT4 immunoassays during pregnancy. Other investigators note that the currently used FT4 immunoassays perform reasonably well under most circumstances, accurately reporting low FT4 levels in thyroid hormone deficiency and high FT4 levels in thyroid hormone excess [6, 7]. In the study by Lazarus et al. [1], of the patients who tested positive, about 5% had both high TSH and low FT4, while the remaining 95% were equally distributed between those with low FT4 and those with high TSH. Given the uncertainty about the accuracy of FT4 measurements in pregnancy, a bias in the selection of patients may have occurred. We do not know if more accurate measurements of FT4, such as dialysate or ultrafiltrate of serum samples employing on-line extraction/liquid chromatography/tandem mass spectrometry, which are available in research labs but not clinically, may have resulted in different study results.

In conclusion, the Antenatal Thyroid Screening and Childhood Cognitive Function study represents a cornerstone in the field of thyroid and pregnancy, but given the above-mentioned critical points, it did not definitively clarify whether a state of mild thyroid impairment is dangerous or not for the neurodevelopment of children.

References

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