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Does replacement therapy for subclinical hypothyroidism in pregnancy provide no benefit to cognitive function in children?

Editors
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This is the conclusion of a multicenter study coordinated at the University of Texas Southwestern Medical Center and published in the NEJM (1)
Women between 8 and 21 weeks pregnant were screened for subclinical hypothyroidism (SH, defined as a TSH level >3.0 UI/L and FT4 within normal range) and for hypothyroxinemia (HT, defined as FT4 <11.0 pmol/L and TSH within normal range). 677 women with SH and 526 with HT were then enrolled in a series of parallel randomized placebo controlled trials run in 15 different centers in the USA. Following randomization, 339 in the SH group received levothyroxine (100 µg) and 338 a placebo; in the HT group, 265 women received levothyroxine (50 µg) and 261 a placebo. Thyroid function was assessed monthly throughout pregnancy, and the levothyroxine dose targeted to a TSH between 0.1 and 2.5 UI/L and a FT4 between 11 and 24.5 pmol/L (depending on the trial), with sham adjustments for placebo. No patient required a dose of levothyroxine superior to 200 µg. The primary outcome was the IQ score at 5 years of age (or at 3 years of age if the 5-year examination was missing) measured with age-specific scales or death at an age of less than 3 years.

Results

At three years of age, children of mothers receiving levothyroxine had a median IQ of 94 (95% CI 91-95) vs. 91 (95% CI 89-93) in the placebo group (p = 0.30). At five years of age, children of mothers with SH receiving levothyroxine had a median IQ of 97 (95% CI 94-99) vs. 94 (95% CI 92-96) in the placebo group (p = 0.71). Similarly non-significant results were observed in children of mothers with HT. Analysis of several secondary outcomes (concerning cognitive, motor and language development) in 649 children of mothers with SH and 507 mothers with HT, also failed to detect any significant difference on the basis of specific evaluation scales.

Discussion

The main goal of this complex study was to test the recommendation of the American College of Obstetrics and Gynecology, which, to this day, does not support universal screening of thyroid function in pregnancy due to limited data on benefit of treatment with levothyroxine. The results of the current study confirm this recommendation, at least in relation to the outcomes investigated.
However, not everybody agrees with the conclusions of the study. In an accompanying editorial, David Cooper, director of the Thyroid Clinic at Johns Hopkins University in Baltimore, and Elizabeth Pearce, of Boston University, contrast the methodology in the current study with that of the 2012 CATSS Study (3). According to the editorialists, the evaluation of the IQ at age 5 (rather than at age 3.5 years as in CATSS) may correlate better with long-term outcomes. The current study also evaluates the positivity of Ab anti TPO (no effect in women receiving treatment or placebo), not investigated in CATSS.
The main critique made by the editorialists is that in the current study, like in CATSS, treatment started relatively late in pregnancy (at 17 weeks), as the thyroid develops between 16 and 20 weeks. Taking into account that treatment with levothyroxine at dosages used in the study is inexpensive and almost without side effects, Cooper et Pearce support the advice of the American Thyroid Association, which suggests the following use of levothyroxine in pregnancy:

a. In every woman with TSH >10 mIU/L
b. In every woman Ab TPO positive if TSH >4.0 mIU/L
c. To be considered in women Ab TPO positive and TSH 2.5-4.0 mIU/L
d. To be considered in women Ab TPO negative and TSH 4.0-10.0 mIU/L
e. Not recommended in women Ab TPO negative and TSH <4.0 mIU/L.

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The guidelines of the European Thyroid Association (ETA) also suggest that levothyroxine « … can be considered in patients with hypothyroxinemia during the first trimester» (5).

References

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