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The Evidence for Performing Universal Screening for Detection of Thyroid Disease in Pregnancy Continues to Be "Soft"

Lazarus JH, Bestwick JP, Channon S, Paradice R, Maina,A, Rees R, Chiusano E, John R, Guaraldo V, George LM, Perona M, Dall'Amico D, Parkes AB, Joomun M, Wald NJ. Antenatal thyroid screening and childhood cognitive function. N Engl J Med 2012;366:493-501.

SUMMARY

Background

Active secretion of thyroid hormone by the fetal thyroid does not start until about 18 to 20 weeks' gestation. Until then, the fetus is dependent on T_4 from the mother for growth and development, including central nervous system maturation. High levels of thyrotropin and/or low levels of FT_4 in women during pregnancy have been associated with impaired cognitive development in their offspring, suggesting that antenatal screening and treatment of thyroid deficiency may be worthwhile.

Methods

The authors conducted a randomized, controlled trial to assess the effects of a high thyrotropin level, a low FT_4 level, or both on cognitive function of the 3-year-old offspring of women who underwent thyroid screening in early pregnancy and received treatment.

Pregnant women were recruited from 10 centers in the United Kingdom and 1 center in Italy. Exclusion criteria were an age of less than 18 years, a gestational age of more than 15 weeks 6 days, twin pregnancies, and known thyroid disease. After blood samples were drawn and sent to a reference lab, the women were randomly assigned to a group whose blood was immediately tested for FT_4 and TSH and who were treated with L-T_4 if the screening results were positive or to a control group whose blood was stored at –40°C and was tested only after delivery. Women were classified as positive if the serum thyrotropin concentration was above the 97.5th percentile, the serum FT_4 concentration was below the 2.5th percentile, or both. Patients in the group who were treated with L-T_4 (starting at 150 µg per day) had thyroid function rechecked 6 weeks after the start of L-T_4 therapy and at 30 weeks' gestation, with adjustment of the dose as necessary. The target thyrotropin level was 0.1 to 1.0 mIU per liter. All women received routine obstetrical care. The primary outcome was the IQ, at 3 years of age, of children of the women who tested positive. Based on the results of a 1999 study by Haddow et al. (1), 22 (5%) of the children of the women who received L-T_4 would have been expected to have an IQ of 85 or less, as compared with 66 children (15%) of women in the control group.

Results

A total of 21,846 women were recruited and underwent randomization; 10,924 were assigned to the screening group and 10,922 were assigned to the control group. The proportion of women who had positive results on screening tests was 4.6% in the group given L-T_4, and 5.0% in the control group. About 5% of women classified as having positive screening results had both a high thyrotropin level and a low FT_4 level. L-T_4 was started at a median gestation of 13 weeks 3 days. Psychological testing was completed in 78.2% of the children of women who tested positive in the group receiving L-T_4, and in 73.3% of the children of women who tested positive in the control group. There were no significant differences between the screening and control groups with respect to gestational age at delivery (median, 40.1 and 40.2 weeks, respectively; P = 0.10), rates of preterm birth (<37 weeks' gestation) (5.6% and 7.9%; P = 0.20), and birth weight (mean, 3.5 kg and 3.3 kg; P = 0.15).

Cognitive Function

The mean standardized IQ in the children of the control group was 100.0 (by definition), and was 99.2 in the children of the women who received L-T_4 (P = 0.40). The proportion of children with an IQ of less

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than 85 was 12.1% in the L-T_4-treated group and 14.1% in the control group (P = 0.39). An analysis adjusting for initial thyrotropin measurements (log-transformed) also did not show a significant association between thyrotropin and IQ. There were no significant between-group differences in the results of other psychological assessments (Child Behavior Checklist [CBCL] and Behavior Rating Inventory of Executive Function, preschool version [Brief-P] scores).

Post hoc analyses were performed in the following subgroups: women with a positive screening results according to TSH level only, women with positive screening results according to FT_4 level only, and women with positive screening results according to both TSH and FT_4 levels, women who began to receive treatment before 14 weeks' gestation, women who began to receive treatment at 14 weeks' gestation or later, women in whom the target TSH level was achieved by 6 weeks after screening, and women in whom the target thyrotropin level was achieved at 30 weeks' gestation. There were no significant differences in IQ scores between the L-T_4-treated group and the control group in any of these subgroup analyses.

Conclusions

The authors found no significant difference in IQ scores between the 3-year-old children born to women who were randomly assigned to the screening group at about 12 weeks' gestation and who were treated for reduced thyroid function before 20 weeks' gestation (median, 13 weeks 3 days) and the children born to women with reduced thyroid function who were randomly assigned to the control group and received no L-T_4 treatment during pregnancy. There were also no significant between-group differences in analyses limited to the women who adhered to treatment. Current guidelines do not recommend routine antenatal screening for hypothyroidism in pregnancy; this study provides support for these guidelines, since the authors found no benefit of routine screening for maternal hypothyroidism at about 12 to 13 weeks' gestation in the prevention of impaired childhood cognitive function.

ANALYSIS AND COMMENTARY

The noninterventional study of Haddow et al. published in 1999 concluded that children of untreated pregnant women with hypothyroidism had a lower IQ score at age 7 to 9 than children from euthyroid mothers (1). The mean (±SD) serum TSH in the women with hypothyroidism was 13.2±0.3 mU/L (geometric means and logarithmic standard deviations) as compared with 1.4 ±0.2 mU/L in control euthyroid mothers (P<0.001), with 9 of 62 women having TSH values over 30 mU/L (1). Serum T_4 and FT_4 were also significantly different between hypothyroid and euthyroid women. In the current study, the median serum TSH in women with hypothyroidism was 3.8 mIU/L in the screening group and 3.2 mIU/L in the women in the control group (not treated) (interquartile ranges, 1.5 to 4.7 and 1.2 to 4.2, respectively).

In the past decade, multiple cohort and observational studies have been published, which have suggested a significant increase in obstetrical complications in mothers with subclinical hypothyroidism or hypothyroxinemia, in areas reported as iodine-sufficient. Most of the women were tested in the first trimester and/or early second trimester of gestation. In the vast majority of the studies, only a single determination of thyroid tests was available for the whole length of the pregnancy (reviewed in 2). The complications most frequently reported were miscarriages and preterm delivery (<37 weeks' gestation), with other complications reported in some but not all studies, including preeclampsia, breech delivery, infants who were small for gestational age, and postpartum bleeding. The suggestion that early screening for detection and treatment of maternal hypothyroidism, with the intent to prevent obstetric and offspring complica-

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tions, became a hot and controversial issue among physicians caring for these patients. Guidelines for the management of thyroid disease in pregnancy were published by other endocrine societies (3,4), with the recommendation for target or case-finding instead of universal screening in the first obstetrical visit, which is also the position of the American Congress of Obstetricians and Gynecologists (5). The lack of justification for universal screening was based on the fact that only a single control study of less than 100 pregnant women was available in the literature, which showed a significant decrease in miscarriage rate and preterm delivery in euthyroid women with evidence of chronic thyroiditis who had been treated with L-T_4, as compared with a nontreated group (6). The authors of the current study acknowledge that other studies have found more specific cognitive impairments associated with maternal hypothyroidism or hypothyroxinemia, among them psychomotor deficit, delays in the development of expressive language, vision abnormalities, and behavioral changes. In addition to the difference in the degree of thyroid dysfunction (only 5% of the women suffered clinical hypothyroidism in the Lazarus study), and IQs were measured at 3 years of age, whereas in Haddow study, testing was done between 7 and 9 years of age.

Additional randomized studies are needed to answer three important clinical questions: (1) Does starting L-T_4 therapy early in pregnancy, in women with subclinical hypothyroidism—and also in euthyroid women with chronic thyroiditis—prevent obstetrical and/or long-term complications in offspring? (2) If so, is universal or case-finding early in pregnancy cost-effective in preventing such complications? and (3) What initial screening tests should be performed: TSH, FT_4 or equivalent, and/or TPO antibodies? In the meantime, physicians treating women of reproductive age should be aware that a significant number of them have symptoms that could indicate thyroid disease, that prompt assessment of thyroid status is in order, and if there is evidence of hypothyroidism, L-T_4 therapy is of potential benefit not only to the patient during the current pregnancy, but also if there is a subsequent pregnancy. At this point, once a woman is pregnant, whether to perform universal screening or case finding is a decision based on personal experience.

— Jorge H. Mestman, MD

References

1. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341:549-55
2. Milanesi A, Brent GA. Management of hypothyroidism in pregnancy. Curr Opin Endocrinol Diabetes Obes 2011;18:304-9.
3. Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011;21:1081-125. Epub July 25, 2011.
4. DeGroot LJ, Abalovich M, Erik K, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab (in press).
5. Committee on Patient Safety and Quality Improvement; Committee on Professional Liability. ACOG Committee Opinion No. 381: Subclinical hypothyroidism in pregnancy. Obstet Gynecol 2007;110:959-60.
6. Negro R, Formoso G, Mangieri T, et al. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 2006;91:2587-91. Epub April 18, 2006.