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Neurodevelopment May Be Entirely Normal in Children Born to Women with Hypothyroidism Who Are Restored to Euthyroidism by Late Pregnancy

Momotani N, Iwama S, Momotani K. Neurodevelopment in children born to hypothyroid mothers restored to normal thyroxine (T_4) concentration by late pregnancy in Japan: No apparent influence of maternal T_4 deficiency. J Clin Endocrinol Metab. February 8, 2012 [Epub ahead of print].

SUMMARY

Background

Thyroid hormone is essential for brain development both before and after birth. Maternal T_4 has been shown to have a crucial role in brain development in fetuses with sporadic congenital hypothyroidism. The importance of maternal T_4 has also been shown in basic studies in fetal neurodevelopment before the onset of fetal thyroid function, which corresponds to the first trimester in humans. Moreover, the correlation between mild maternal T_4 deficiency at 12 to 17 weeks' gestation and disturbance of neurodevelopment in progeny has been shown in case–control studies in The Netherlands and the United States. These observations have given rise to the perception that maternal hypothyroidism or T_4 deficiency in early pregnancy leads to a defect in neuropsychological development. On the other hand, the absence of intellectual impairment among children, irrespective of the severity of T_4 deficiency in the mother in early pregnancy after T_4 normalization by late pregnancy, has been reported from Japan. This points to uncertainty about whether the neurologic impairment is a result of reduced availability of maternal T_4 in early pregnancy. The authors reported five cases showing no apparent effect of maternal T_4 deficiency on neurodevelopment in progeny in whom low T_4 levels had been corrected by late pregnancy.

Methods

Five women with overt hypothyroidism detected at 6 to 16 weeks' gestation initiated T_4 treatment. The serum TSH levels at detection ranged from 23.3 to 657 mU/L and the serum FT_4 from 0.09 to 0.66 ng/dl. In four women, euthyroidism was restored by the 20th week. One remained in a subclinical hypothyroid state. Developmental scores of their children were evaluated between 25 months and 11 years of age by either the Tsumori-Inage Infant's Developmental Test or the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) and compared with those of siblings with no exposure to maternal hypothyroidism.

Results

Initial serum TSH and FT_4 levels were monitored at 2- to 6-week intervals; they normalized by 20 weeks in 4 patients; in the other woman, subclinical hypothyroidism remained for the rest her gestation. The WISC-III scores of 3 children were compared with their 3 siblings born when mothers were euthyroid during a subsequent pregnancy; the scores were within the normal range and not significantly different between the siblings. In the other 2 infants, the score on the Tsumori-Inage infant psychomotor development test was within the normal range at age 25 and 35 months. Their siblings were not tested.

Conclusions

In iodine-sufficient areas, maternal T_4 deficiency in early pregnancy does not necessarily affect neurodevelopment. However, early detection by routine screening would be crucial where recovery from hypothyroidism by late pregnancy is essential for normal brain development. Therefore, other factors that could potentially alter neurodevelopment, such as iodine deficiency, must be investigated.

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ANALYSIS AND COMMENTARY

In this study, IQ and DQ (development quotient) scores indicated no apparent neurodevelopmental deficit in children whose mothers had overt hypothyroidism during the first trimester of pregnancy and were restored to normal serum T_4 levels by late pregnancy. Haddow et al. (1) reported lower IQs in children of untreated pregnant women with hypothyroidism. At about the same time, Pop et al. (2) described impaired psychomotor development in infants of women with hypothyroxinemia who had serum TSH levels within the reference range. In the Pop study, children of women with hypothyroxinemia with FT_4levels below the 5th percentile (11 mothers) and below the 10th percentile (22 mothers) at 12 weeks' gestation were evaluated at 10 months of age using the Bailey Psychomotor Development Index scale; they had significantly lower scores as compared with children of mothers with higher FT_4 values. Since this study was carried out in an area with iodine sufficiency, there was no clear cause to explain isolated cases of hypothyroxinemia. It is well known that in areas of chronic iodine deficiency, serum iodine and T_4 are low, with a corresponding increase in T3 production (3). Other studies from areas of iodine deficiency describe deleterious neurocognitive defects in offspring of women with hypothyroxinemia (4). In Japan in 1994, Liu et al. (5) studied IQs of eight children born of women with severe hypothyroidism (mean [±SD] serum TSH, 116±59 μU/ml; FT_4, <0.5 ng/dl) detected during the 5th to 10th week of gestation and compared them with IQs of their siblings born when mothers were euthyroid. All women with hypothyroidism had normal FT_4levels by 28 week' gestation. The IQ scores of these children at 4 and 10 years were normal and comparable to their siblings studied at comparable ages. It is surprising that this study published in an American journal was not cited by Haddow or Pop in their publications. Momotani et al. now confirm the original observation by Liu et al (both populations were from the same geographic area in Japan); the degree of hypothyroidism was much more severe in the patients reported by Liu et al. (5) and Momotani than in those included in the series by Haddow et al. (1) and Pop et al. (2). Furthermore, in a 2003 study by Pop et al. (6), no apparent neurodevelopment delay was seen in children when maternal FT_4 levels spontaneously increased after the first trimester. As suggested by the authors, the discrepancies between other studies and their own may reside in the amount of dietary iodine intake, which is very high in Japan (7). It was recently reported that iodine concentration is low in the formula given to premature infants in the Boston area (8). The importance of iodine replacement in women of childbearing age is underestimated; it was proposed that proper iodine supplementation should be started years before conception in order to achieve normal thyroid function in early pregnancy (9).

— Jorge H. Mestman, MD

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