Maternal Hypothyroidism and Child Development

A Review

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**Key Words**
Maternal hypothyroidism · Screening for hypothyroidism · Mental retardation in children · Prevention of brain damage

Combined maternal and fetal hypothyroidism, due to either endemic iodine deficiency or autoimmune thyroiditis is associated with the fetal neurodevelopmental problems of classic cretinism [1–4]. The relative contributions of maternal and fetal deficiencies to the CNS developmental problems have not been established. Pharoah et al. [2] reported a correlation of maternal T4 levels, but not of T3, with cognitive and motor adevelopment of the offspring. In cretinism associated with autoimmune disease, central nervous system problems in the offspring have been described only in the rare instances of thyroid deficiency in the mother associated with transient hypothyroidism in the neonate. Such problems have been described in endemic disease when the newborn was not hypothyroid but it is impossible to rule out transient fetal hypothyroidism in either endemic or in autoimmune disease. Treating the transient hypothyroidism in the offspring even from birth does not lessen the CNS problems.

Early reports on hypothyroidism in pregnancy commented chiefly on the rarity of its occurrence and the poor obstetrical outcomes [5, 6]. Some of the surviving offspring were said to be mentally retarded, but there is no way to distinguish these cases retrospectively from the cases of combined maternal and fetal autoimmune hypothyroidism subsequently recognized [3, 4, 6]. In 1962, Greenman et al. [7] reported a study of 19 pregnant women with confirmed or suspected hypothyroidism. They, too, were more interested in obstetric problems but did follow the surviving offspring for 8–12 months. In this study, no IQ scores were reported presumably because the children were too young. There were 7 women whose hypothyroidism had been diagnosed and whose treatment had begun before pregnancy. All their 5 surviving infants were considered to be mentally normal. Seven women who were first suspected of being hypothyroid during their pregnancies had the diagnosis verified by low butanol-extractable iodine (BEI) concentrations. Four of their 5 surviving infants were considered to be mentally retarded. Two of the brain-damaged infants were premature and one had multiple gross congenital anomalies. In retrospect, 2 infants were probably hypothyroid as indicated by low BEI concentrations. The last 6 mothers were suspected of being hypothyroid because each had a goiter, but they all had BEI concentrations in the normal range for pregnancy. They had no obstetric problems and their children were considered to be normal.

Man and co-workers [8, 9] first suggested in 1969 that mild maternal hypothyroidism alone was associated with
lower IQs in the offspring. They reported that the children of mothers with inadequately treated or untreated hypothyroidism had lower IQs than did the children of either adequately treated hypothyroid or control mothers. Some of the subjects were screened using BEI measurements, and others of women were tested by BEI measurements because of clinical signs suggestive of hypothyroidism.

Later investigators reported no increase in mental retardation associated with mild hypothyroidism. They discounted the work of Man because she used the subsequently outdated measurement of BEI for the diagnosis of hypothyroidism. Of more concern is possible selection bias as a result of inappropriate decisions as to adequacy of treatment in Man’s studies.

In the subsequent studies of later authors, the women were treated during gestation frequently but IQs of offspring were infrequently measured [10–13]. Again it is likely that many of the mothers had autoimmune hypothyroidism. In one study, that of Liu et al. [12], the 8 mothers were found to be hypothyroid at 5–10 weeks of station and treated at that time. Seven of the 8 had completely normal hormonal values at 13–20 weeks of gestation. The eighth did so at 28 weeks. The 8 children all had normal neonatal screening TSH results and had normal IQs at 4–10 years. Rolland et al. [13] reported results from a questionnaire sent to all females diagnosed with congenital hypothyroidism in their hospital from 1950 to 1980. Eleven of the 22 responders had had 17 pregnancies. Two resulted in spontaneous abortions and 2 liveborn infants died in the first month of life. Treatment of only one of the mothers was discontinued during pregnancy. The 13 surviving infants were reported to have normal psychomotor development at 6 months to 21 years of age.

The study of Pop et al. [14] is interesting because they reported lower IQs in the children of mothers with antibodies to thyroid peroxidase but normal thyroid hormonal values at 32 weeks gestation. They suggested that the antibodies did not cause the CNS problems but were an epiphenomenon. We presume that the mothers had had earlier gestational hypothyroidism. The possibility remains that the antibodies were associated with temporary, and thus, undiagnosable, fetal autoimmune hypothyroidism as well.

Klein et al. [15] reported TSH concentrations in 2,000 blood specimens from women drawn at 17 weeks gestation for alpha-fetoprotein screening. TSH concentrations were ≥ 6 mU/l in 2.4% and ≥ 12 mU/l in 0.3%. None was symptomatic, but FT4 concentrations were ≥ 2 standard deviations below the normal mean in 60% of those with TSH concentrations ≥ 99.7th percentile. Mean age of the hypothyroid mothers was greater than that of the control mothers, 29.1 vs. 26.9 years (p < 0.02), paralleling the increasing incidence of hypothyroidism with age in the general population. These findings were verified in an unpublished study by the same investigators, of 10,000 women, 2.2% of whom had TSH concentrations ≥ 6 and 0.3% had concentrations ≥ 12 mU/l. FT4 concentrations were ≥ 2 SD below the control mean in 40% of those with TSH concentrations ≥ 99.7th percentile. Tests for antibodies to TPO were positive in 67% of the mothers with TSH concentrations ≥ 99.7th percentile. There was an increased incidence of poor obstetric outcomes in this group of hypothyroid mothers with significant increases in spontaneous abortions and intrauterine fetal deaths. There were statistically insignificant increases in overall deaths and premature births as well.

A report was presented in Firenze at the 37th meeting of the European Society for Pediatric Endocrinology in 1998 which essentially verified Man’s suggestion that children born to mothers with untreated hypothyroidism had lower IQs than children of normal mothers or mothers with adequately treated hypothyroidism [16, 17]. In this last study, 25,000 pregnant women were screened for hypothyroidism retrospectively. TSH concentrations were measured in sera obtained at a mean of 17 weeks of gestation for routine purposes which had been frozen and stored for 8 years. The women were divided into 3 groups comprised of 14 women with a previous clinical diagnosis of hypothyroidism who had been treated before and throughout pregnancy, 48 women whose hypothyroidism was untreated during pregnancy although one had been treated for a year before conception, and 124 matched control mothers whose TSH concentrations were below the 98th percentile. Their children underwent psychometric evaluations at 8 ± 0.5 (SD) years of age.

There were no differences among the 124 control, 14 treated, and 48 untreated hypothyroid mothers in maternal and paternal occupations, paternal education, and Hollingshead Indices in addition to the demographic items by which the controls had been matched in the process of selection (maternal education, maternal age, and birthdate and sex of the child).

None of the children had either permanent or transient congenital hypothyroidism on neonatal screening or clinically on follow-up at 8 years. One hundred and twenty of the control mothers and 45 of those with untreated hypothyroidism were able to be contacted 10 years following delivery. 58% of the previously untreated hypothyroid mothers and 4% of control mothers had developed sufficient signs and symptoms of hypothyroidism to have been
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Table 1. TSH, T4, FT4, and antibodies to TPO in sera at 17 weeks of gestation of 124 control women, 14 treated hypothyroid women, and 48 untreated hypothyroid women

<table>
<thead>
<tr>
<th>Mothers</th>
<th>TSH mU/l*</th>
<th>T4 nmol/l**</th>
<th>FT4 pmol/l**</th>
<th>Anti-TPO %</th>
</tr>
</thead>
<tbody>
<tr>
<td>124 control</td>
<td>1.33 (1.2, 1.5)</td>
<td>136±18</td>
<td>13±3</td>
<td>12</td>
</tr>
<tr>
<td>14 Rxed hypothyroid</td>
<td>17.81 (12.7, 25.3)</td>
<td>98±35</td>
<td>9±2</td>
<td>79</td>
</tr>
<tr>
<td>48 non-Rx hypothyroid</td>
<td>12.10 (9.7, 15.1)</td>
<td>98±22</td>
<td>9±2</td>
<td>78</td>
</tr>
</tbody>
</table>

p control vs. Rxed 0.0005 0.0005 0.0005 0.0005
p control vs. non-Rx 0.0005 0.0005 0.0005 0.0005
p Rxed vs. non-Rx NS NS NS NS

* Geometric mean (95% confidence limits).
** Mean ± SD.

p values are for the significance of differences on dummy variable regression analysis for the hormones and on Fisher’s exact test for TPO antibodies. NS = Not statistically significant. Assays for FT4 and TPO antibodies were not made for one mother in each hypothyroid group because of insufficient specimens.

diagnosed clinically at a median time of 5 years postpregnancy. The percentage over the 10 years in the control mothers was what would be expected from the Whickham study [18].

Table 1 compares concentrations for TSH, T4, FT4, and for presence of antibodies to TPO in maternal sera at 17 weeks of gestation of the control mothers with those of the treated and of the untreated hypothyroid mothers.

Figure 1 depicts the means and 95% confidence intervals for full-scale IQ scores in children of 124 control mothers (cross-hatched rectangle) and 14 treated (clear rectangle) and 48 untreated hypothyroid mothers (dotted rectangle).

Table 2 compares the outcomes for children born of control mothers and of treated and untreated hypothyroid mothers for school performance by Fisher’s exact test and for 10 psychometric tests using dummy regression analyses.

The scores of children of untreated hypothyroid mothers were poorer in all of the 11 outcomes than those of the children of control mothers. The differences were statistically significant for all but the scores for the VMI test.

The test scores for the children whose mothers were treated before and during pregnancy were poorer than those of children of control mothers only in the computer test of attention. The children whose mothers were treated did better than did the children of control mothers in the other 9 tests albeit insignificantly. They also did better than the children of untreated hypothyroid mothers. The last differences were statistically significant in only 4 of the tests. The paucity of children of treated mothers and the large variances for their outcomes should be noted. These may have obscured the significance of the differences in some of the comparisons involving children of treated mothers and exaggerated others.

Compared with the children of control mothers, twice as many children of untreated hypothyroid mothers had an IQ >1 standard deviation below the control mean, 35 vs. 18%, p = 0.018 and four times as many had IQs >2

![Fig. 1. Means and 95% confidence intervals for full scale IQ scores in children of 124 control mothers and of 14 treated and 48 untreated hypothyroid mothers. Cross-hatched rectangle = IQs of children of control mothers; clear rectangle = IQs of children of treated hypothyroid mothers; dotted rectangle = IQs of children of untreated hypothyroid mothers. The means and SEs are given above each rectangle. p values are the significance of the differences between each pair of results on dummy variable regression analysis.](image-url)
**Table 2. Outcomes for children of 124 control women and of 14 treated hypothyroid and 48 untreated hypothyroid women**

<table>
<thead>
<tr>
<th>Mothers</th>
<th>VIQ</th>
<th>PIQ</th>
<th>FSIQ</th>
<th>FREE</th>
<th>CPT</th>
<th>LANG</th>
</tr>
</thead>
<tbody>
<tr>
<td>124 control</td>
<td>108±1.2 SEM</td>
<td>105±1.2</td>
<td>107±1.1</td>
<td>102±1.1</td>
<td>3.3±0.5</td>
<td>105±1.0</td>
</tr>
<tr>
<td>14 Hypo Rxed</td>
<td>111±3.3</td>
<td>109±4.1</td>
<td>111±3.3</td>
<td>103±3.6</td>
<td>8.2±1.7</td>
<td>106±3.0</td>
</tr>
<tr>
<td>48 Hypo Non-Rx</td>
<td>101±2.3</td>
<td>99±2.2</td>
<td>100±2.2</td>
<td>97±2.1</td>
<td>5.6±0.9</td>
<td>100±2.0</td>
</tr>
<tr>
<td>p Hypo Rxed vs. control</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>p Hypo NoRx vs. control</td>
<td>0.01</td>
<td>0.01</td>
<td>0.004</td>
<td>0.03</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>p Hypo Rx vs. non-Rx</td>
<td>0.012</td>
<td>0.02</td>
<td>0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mothers</th>
<th>READ</th>
<th>VMI</th>
<th>PEG dom</th>
<th>PEG nond</th>
<th>SCHOOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>124 control</td>
<td>101±1.7</td>
<td>97±1.0</td>
<td>82±1.4</td>
<td>89±1.5</td>
<td>18%</td>
</tr>
<tr>
<td>14 Hypo Rxed</td>
<td>102±4.4</td>
<td>102±4.5</td>
<td>80±4.4</td>
<td>88±5.0</td>
<td>29%</td>
</tr>
<tr>
<td>48 Hypo NoRx</td>
<td>95±2.3</td>
<td>94±1.6</td>
<td>88±2.7</td>
<td>97±3.2</td>
<td>33%</td>
</tr>
<tr>
<td>p Hypo Rxed vs. control</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>p Hypo non-Rx vs. control</td>
<td>0.05</td>
<td>NS</td>
<td>0.05</td>
<td>0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>p Hypo Rx vs non-Rx</td>
<td>NS</td>
<td>0.03</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*p values for significance of differences on dummy variable regression analysis for the 10 tests and on Fisher's exact test for incidence of school problems, a categorical variable. NS = not statistically significant. VIQ = Verbal IQ-WISC III; PIQ = performance IQ-WISC III; FSIQ = full scale IQ-WISC III; FREE = freedom from distractibility-WISC III; CPT = continuous performance test, a computer test of attention; LANG = quotient for language development, TOLD; READ = Peabody reading test, combined recognition and comprehension; VMI = visual-motor integration test; PEG dom = pegboard performance test for dominant hand; PEG nond = pegboard performance test for nondominant hand; SCHOOL = incidence of one or more serious school problems, i.e. extra year in grade or in transition class, or being in a special class for retarded learners.*

Standard deviations below the control mean, 13 vs. 4%, *p = 0.08* (Fisher’s exact tests). The child of one of the 14 treated mothers (7%) had an IQ >1 SD below the control mean and none had an IQ >2 SD below the control mean.

Regression analyses of children’s IQs and FT4 concentrations of their mothers using treatment status as a covariate were significant at *p = 0.025*. This supports the hypothesis that severity of maternal hypothyroidism correlates with outcomes in the offspring. There was no correlation of cognitive outcomes with TPO antibodies.

There were 46 hypothyroid women, treated and untreated, with TSH concentrations ≥99.7th percentile. Assuming they were representative of the total group of 75 with such TSH concentrations, at least one per thousand of all newborns are at risk of having an IQ >1 SD below the control mean associated with maternal hypothyroidism. This would suggest that if women can be screened before or early enough in pregnancy, the beneficial effects on cognition would be tenfold greater than those provided by neonatal congenital hypothyroidism screening [19].

The experience of this study suggests that the increased need for thyroxine in pregnancy is commonly not met. It is clear from Haddow’s report that untreated subclinical maternal hypothyroidism is associated with poor cognitive outcomes in the offspring whereas children of previously clinically diagnosed hypothyroid women who had thyroxine replacement therapy before and during pregnancy do as well as children of control mothers. The obvious possibility that hypothyroidism is the cause of the cognitive deficits and that thyroxine therapy prevents this is the most likely explanation. Maternal hypothyroidism could act directly by causing fetal hypothyroidism or indirectly by affecting placental function, for instance. There is, however, a question about the relation of maternal treatment to childhood outcomes. The treated mothers’ mean hormonal values at 17 weeks of gestation were no better than those of untreated women. The present authors hypothesize that maternal thyroid function was normal in the treated mothers at a critically earlier time before the required maternal T4 replacement dose increased pari passu with the increasing concentrations of...
Maternal hormonal levels are expected to become irrelevant sometime after 10–12 weeks of gestation if the fetal thyroid produces the normal increasing amounts of thyroxine absent autoimmune or congenital fetal hypothyroidism [4, 21].

The data suggest that the damage to the fetal CNS most likely occurred early in pregnancy presumably before fetal thyroxine production was significant. In sporadic congenital hypothyroidism, measurable brain damage occurs only when the child is no longer protected by maternal thyroid hormone since early and adequate postnatal treatment is associated with normal IQs in the progeny [22]. In cretinism of either etiology, the damage must come earlier since treatment of the neonate from the first day of life does not prevent it. Treatment of the mother with autoimmune hypothyroidism throughout pregnancy will prevent fetal brain damage, however [4]. Most authors suggest that fetal brain damage in cretinism occurs at least as early as the first trimester [23, 24]. However, Cao et al. [25] have suggested that the damage can be prevented in endemic disease by treating the mother with iodine as late as the second trimester. The problem with this is that a fourth of the mothers who were treated in the second trimester in that study had also had iodized oil treatments within 6 months of the pregnancy and their infants’ IQs are not identified separately in Cao’s report.

Conclusions

We believe that the literature reviewed indicates that: (1) Maternal hypothyroidism, even if subclinical, interferes with normal fetal brain development. The incidence of cognitive deficiency in all newborns from maternal hypothyroidism is much greater than that due to sporadic congenital hypothyroidism before the advent of neonatal hypothyroidism screening. (2) This fetal CNS damage is preventable by maternal thyroxine therapy. It therefore follows that mothers should be screened for hypothyroidism and treated before or as early as possible during pregnancy.

References

23 Pharoah POD, Butterfield HH, Hetzel BS: Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. Lancet 1971;i:308–310.