Maternal Hypothyroxinemia: Psychoneurological Deficits of Progeny*†

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ABSTRACT

Maternal thyroid function was evaluated clinically, by reproductive history, and by serial measurements of serum butanol-extractable iodine (thyroxine-like iodine), two before and two after 24 gestational weeks during 1,349 pregnancies. Three percent of the women were hypothyroxinemic. Developmental, intellectual, and motor abilities of progeny born to (Group I) 210 euthyroxinemic, (Group II) 15 hypothyroxinemic given adequate thyroid replacement therapy, and (Group III) 21 inadequately treated hypothyroxinemic women were compared. The groups of mothers exhibited no significant differences in intelligence, years of education, or chronological age. Mean developmental and intellectual scores at eight months, four and seven years of Group II progeny evidenced remarkably consistent similarity to scores of siblings and controls. At each age, mean developmental and intellectual scores were lower for Group III progeny, and motor scores of the latter were lowest. Some progeny of Group II mothers, treated only after 12 or 29 weeks, failed the ball catch and line walk tests; some had strabismus and other ocular disturbances. Could these deficits have originated with maternal hypothyroxinemia during first semester weeks before the thyroid-pituitary axis matures? Now in 1990—1991, early findings fit into the modern concepts of significant maternal gestational transfer of thyroxine to the fetus. The authors encourage prenatal and/or early gestational screening for maternal hypothyroxinemia and urge prescription of adequate thyroid replacement therapy for hypothyroxinemic women.

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Preface

Presentations of Dr. Gabriella Morreale de Escobar at several international symposia on congenital hypothyroidism and data of other pediatric endocrinologists\(^5,14,17,18,22,24,30,31,35\) stimulated this review. She emphasized a "once-and-only"\(^30(p37)\) period for development of the mammalian brain. During the most active phase of brain growth and differentiation, adequate amounts of thyroid hormones are essential for sequences of maturational changes. Fetal production of thyroid hormones is major in directing brain development, although recent evidence points to the need for maternal euthyroidism. The timetable for arrival of neurons, their multiplication and differentiation, the formation of glial cells, and myelinogenesis may vary in different regions of the brain.\(^30(p29)\)

Either a deficiency or an excess of thyroid hormones at certain hours of the timetable may change cell differentiation. Without the organizing effect of thyroid hormones, portions of the brain "grow into a tangled mass of poorly insulated, poorly connected neurofil."\(^30(p45)\)

Stages of development of the human central nervous system (CNS) before 10, 12, or 14 weeks are dependent on thyroid hormones. In reference to iodized oil injections, Morreale wrote, "Treatment before pregnancy or during the first trimester appears to be necessary to eradicate neurological cretinism."\(^30\) The role of maternal thyroxine for fetal CNS development is reinforced by quotes from *Thyroid. A Special Issue Dedicated to Life and Achievements of Dr. Sidney H. Ingbar*, with these quotes from Schussler.\(^39\)

"Although early studies indicated that the free T4 might be low in pregnancy, it is probably normal in the second and third trimesters and somewhat elevated in the first trimester."\(^40\)\(^-\)\(^39(p27)\)

"There is increasing evidence that physiologically significant entities of thyroid hormone are transferred from the maternal to the fetal circulation.\(^44,45\)\(^-\)\(^38(p27)\)

"As pointed out by Ekins,\(^9\) a maternal source of thyroid hormone is likely to be of greatest importance before fetal thyroid hormone secretion begins. Thus, the hCG-dependent increases of maternal T4 and T3 in the first trimester may be of physiologic significance to the fetus."\(^39(p28)\)

The importance of thyroid hormones for development of the CNS during the first trimester of human gestation and the role of maternal thyroxine for fetal brain development become apparent.

Introduction

The actual data that three percent of women in 1,349 pregnancies were hypothyroxinemic, and that some progeny of inadequately treated hypothyroxinemic women had low IQs and neuropsychological deficits were reported in 10 papers published 1964 to 1976.\(^27,28\)

Data on pregnancies of two groups of 375 women from 97 pregnancies were compared. Group I included 97 pregnancies of 375 control euthyroxinemic women. Group II included 97 pregnancies of 375 hypothyroxinemic women. The incidence of abortions, prematurity, stillbirths, major anomalies, and offspring with subsequent retardation was 26 percent for the control women but 36 percent for the hypothyroxinemic women.\(^28(VI)\) Niswander reported a high incidence of stillbirths of hypothyroid women.\(^34\) Recently, Lazarus and Walker began a worldwide survey of the possible relationship between various congenital anomalies and congenital hypothyroidism.\(^26\)

Some thyroidologists doubted our findings and kept repeating that thyroid hor-
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Mones do not cross the placenta. The NATO Advanced Research Workshop on Congenital Hypothyroidism in Brussels, Belgium, May, 1988, 14 and the study by Vulsma et al in 1989 44 revolutionized the old widely published hypothesis of placental impermeability to thyroid hormones. Vulsma and coworkers demonstrated that in late gestation considerable amounts of T4 are transferred from the mother to her hypothyroid fetus. Larsen 25 reviewed the findings of Vulsma and cohorts 44 and referred to substantial transplacental passage of T4 when T4 cannot be synthesized by the fetal thyroid. Vulsma and coworkers dealt with cord serum and placental transfer of T4 to hypothyroids at term. 44 Most newborns with congenital hypothyroidism and inability to synthesize T4 are asymptomatic at birth. This phenomenon has been assumed to result from substantial placental transfer of maternal T4 to the fetus during an appreciable length of gestation. The findings of Vulsma et al 44 supported our data of 20 years ago. Even Fisher acknowledges that in humans thyroxine "clearly crosses the placenta." 20

Subjects and Methods

The subjects in this longitudinal study were all participants in the Collaborative Perinatal Project of the National Institute of Neurological Diseases and Stroke. 6,7,8,9,10,11 Prenatal examinations of euthyroxinemic and hypothyroxinemic gravidae were conducted at the Providence Lying-In Hospital from 1962 to 1967. Maternal thyroid function was evaluated clinically by reproductive history and by serial measurements of serum butanol-extractable iodines (BEIs) (thyroxine-like iodine) 28 two before and two after 24 gestational weeks during 1,349 pregnancies. 28 (1-IX) Women in the adequately treated hypothyroxinemic group had two low BEIs before 24 weeks and thyroid replacement therapy* at a time interval begun at 12 or 29 gestational weeks. Women in the inadequately treated hypothyroxinemic group were those with two low BEIs but not given adequate replacement therapy. The original (1957) definition of serum iodine compounds measured in the BEI is as follows: 27,28 (1)

"To claim that serum BEI determinations are more precise than PBI determinations implies that the exact chemical nature of the organic iodine compounds included in measurement of the BEI is more accurately delineated than is the nature of the iodine compounds precipitated with protein. "Thyroxine-like" (1, 6, 9) is the best description of the organic iodine compounds which are included in BEI measurements, in spite of the results of recent investigations of analogues of thyroxine and investigations of thyroxine-binding to proteins (16). Recoveries of iodine from thyroxine in aqueous alkaline solution alone, or when added to serum in vitro, were between 88 and 103 per cent—adding the amounts found in 1 ml of serum (1). Triiodothyronine, triiodothyroacetic acid and tetraiodothyroacetic acid added in vitro to serum yielded recoveries of iodine which were as complete as those from thyroxine. However, when triiodothyronine in maintenance doses was administered in vivo, no increase in the concentration of serum BEI could be detected. Moreover, when as much as 32 gamma per 100 ml. of diiodotyrosine iodine or 1,000 gamma per 100 ml. of inorganic iodine was added in vitro to serum (1), none was recovered. Ingbar et al. (17) in their study of butanol-extractable 131I found similar percentile recoveries of thyroxine 131I and virtual exclusion of the 131I linked with potassium iodide or diiodotyrosine. In our original SPI studies (3), 84 per cent of the iodine of diiodotyrosine was recovered. Thus there is a quantitatively important difference between the specificity of the BEI as compared with the SPI determination. The BEI technique does not eliminate contamination from organic iodine compounds 2 given for diagnostic or therapeutic purposes (9)."

2 See Appendix for essential technique in obtaining sera for BEI determinations.

This study was prospective with thyroid replacement therapy being provided only to gravidae, not to their progeny

* Proloid generously donated by the Warner Lambert Company, Morris Plains, NJ.
after birth. T-tests demonstrated no significant differences between the adequately and inadequately treated groups of hypothyroxinemic women in maternal intelligence quotients (T = 1.28 not significant), years of education (T = 0.29 not significant), or chronological ages (T = 0.90, not significant).28(VIII,IX)

Psychological examinations of the progeny were conducted at the Brown University Child Development Study according to protocols for eight month, four year, and seven year examinations specified by the Collaborative Perinatal Project. Procedures for administration and scoring were as prescribed in the manuals of specific assessments.6,7,8,9,10,11,45 At eight months, the mental and motor scales of the research version of the Bayley Scales were administered.28(V) At four years, the Stanford-Binet Intelligence Scale, Form L-M,40 as well as fine and gross motor tasks, were administered.28(VII) The Wechsler Intelligence Scale for Children (WISC)45 and the Bender Visual-Motor Gestalt Test were administered at seven years. All examinations were administered and scored without the examiner’s knowledge of the thyroid status of the mother or the developmental history of the child.28(IX)

Results

INCIDENCE OF MATERNAL HYPOTHYROXINEMIA THREE PERCENT

Figures 1, 2 and 3 are reproduced by courtesy of The C. V. Mosby Company.* In figures 1 and 2 are represented 304 serial, gestational serum BEIs of euthyroxinemic women aged 35 and over and 24 BEIs six or more weeks after delivery. Outer solid lines show means ± 2 S.D. for 164 serial serum BEIs during pregnancies of 30 control euthyroxinemic women aged 18 through 34 years.28(I) Shaded areas demonstrate these values. Graphs for 449 gestational BEIs and 47 values at least six weeks after delivery of 94 younger euthyroxinemic women showed similar distributions28(II) and are not reproduced here. All pregnancies were uncomplicated with deliveries of living neonates, classified normal, and weighing at least 2500 grams. To summarize: 917 BEIs of euthyroxinemic pregnant women fell within the gray areas of figures 1 and 2. (For 164 see reference 28(I) and for 753 see reference 28 (II.) In contrast are the BEIs in figure 3 during 39 pregnancies of hypothyroxinemic women before adequate thyroid replacement therapy.28(V) Scales for minimum and maximum are plotted slightly but insignificantly differently. Note the BEIs in figure 3 below the minima of figures 1 and 2. The incidence of hypothyroxinemia as shown in figure 3 illustrates our meaning of the term hypothyroxinemia and will be compared with data of Volpe,4 Solomon,† Tunbridge,41 and Glinoer21 in the discussion. The overall contrast between figure 3 and its counterparts, figures 1 and 2, is obvious.

PSYCHOLOGICAL TESTS ON PROGENY

In table I are mean developmental and intelligence quotients of the progeny at eight months,28(V) four years,28(VII) and seven years.28(VIII,IX) At eight months, the mean developmental quotients on the mental and motor scales of the Bayley Scales were essentially identical for the infants of the euthyroxinemic and adequately treated hypothyroxinemic women. Scores of progeny of inadequately treated hypothyroxinemic women were significantly lower than those of children of euthyroxinemic women.28(V,VII,IX)

Incidence of normal vocabulary and speech at four years among progeny of

* St. Louis, MO.
† Personal communication to EBM.
adequately treated hypothyroxinemic women was 71 percent; among progeny of euthyroxinemic women, 63 percent; and among progeny of inadequately treated hypothyroxinemic women, 44.5 percent. Almost 75 percent of the progeny of adequately treated hypothyroxinemic women were considered to have normal vocabulary and speech, yet less than half of the progeny of inadequately treated hypothyroxinemic women were rated as normal in these areas.

At four and seven years, the highest mean IQs were obtained by the progeny of adequately treated hypothyroxinemic women with the next highest mean obtained by progeny of euthyroxinemic women and the lowest mean quotient obtained by progeny of inadequately treated hypothyroxinemic women. The difference between the mean IQ quotients of the progeny of the two hypothyroxinemic groups was significant. T was 1.70 and P < 0.05. A most remarkable aspect of table I is the stability of quotients among the three groups of progeny over time and with three instruments of assessment but especially the consistency of quotients for the progeny of adequately treated hypothyroxinemic women.

A distribution of the WISC full scale quotients at seven years (end of table I) included more quotients in the ranges below 80 and 80 to 109 with fewer quotients in the 110 or more range among the progeny of euthyroxinemic and inadequately treated hypothyroxinemic women than expected. The incidence of quotients in the 80 to 109 range for progeny of adequately treated hypothyroxinemic women was less than expected.
because of the very high incidence of quotients in the 110 or more range. No progeny of adequately treated hypothyroxinemic women obtained a quotient below 80 while no progeny of inadequately treated hypothyroxinemic women obtained a quotient of 110 or more. At both four and seven years, progeny of the hypothyroxinemic inadequately treated women (Group III) were poorest in performance of motor skills.

Three hypothyroxinemic women had two children participating in the study with one born after adequate maternal thyroid treatment and one after inadequate thyroid treatment.28(IX) Progeny of adequately treated hypothyroxinemic pregnancies obtained a mean fullscale IQ at seven years of 103.0 whereas the siblings of inadequately treated pregnancies obtained a mean IQ of 83.0. The difference in mean full scale quotients is surprisingly large (more than 1 S.D.) since, in general, siblings tend to have more similar quotients. All progeny of adequately treated pregnancies were classified as overall normal at seven years of age, while none of their siblings were so classified.

PLACENTAS

Only weights, not gross and not microscopic examinations, were available for placentas of 31 euthyroxinemic (Group I), of 11 adequately treated hypothyroxinemic (Group II) and of 14 inadequately treated hypothyroxinemic pairs (Group III) as shown in table II. Placental weights of Groups I and II ranged from
FIGURE 3. Gestational BEIs of 39 hypothyroxinemic women. The open area between minimum and maximum gestational BEIs for euthyroxinemic women mirrors the gray areas of figures 1 and 2 of gestational BEIs of euthyroxinemic women.\textsuperscript{28(i)} Symbols on the BEI determinations identify some signs or symptoms during 24 of the 39 pregnancies. Symbols are located at value of serum BEI. 4-T, Previous thyroidectomy. 3-H, Clinical hypothyroidism. 10-G, Low TBG (These included consecutive values on the same women, not the incidence of low TBGs).\textsuperscript{28(II)} 7-R, Previous reproductive difficulties.\textsuperscript{28(V)}

**TABLE I**

<table>
<thead>
<tr>
<th>Psychological Tests on Progeny</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Mother Group</th>
<th>No.</th>
<th>Mental</th>
<th>Motor</th>
<th>No.</th>
<th>Mean</th>
<th>No.</th>
<th>Mean</th>
</tr>
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<tbody>
<tr>
<td>Euthyroxinemic</td>
<td>1</td>
<td>242</td>
<td>101</td>
<td>104</td>
<td>227</td>
<td>99.5</td>
<td>210</td>
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<td>Hypothyroxinemic adequate therapy</td>
<td>II</td>
<td>29</td>
<td>102</td>
<td>104</td>
<td>22</td>
<td>102.0</td>
<td>15</td>
</tr>
<tr>
<td>Hypothyroxinemic inadequate therapy</td>
<td>III</td>
<td>55</td>
<td>95</td>
<td>98</td>
<td>23</td>
<td>93.0</td>
<td>21</td>
</tr>
</tbody>
</table>

WISC – Wechsler Intelligence Scale for Children.
TABLE II
Placental Weights and Birth Weights

<table>
<thead>
<tr>
<th>Mother Group</th>
<th>No.</th>
<th>Birth Weight</th>
<th>Placental Weight</th>
<th>Birth Weight</th>
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<tr>
<td></td>
<td></td>
<td>Mean Gram</td>
<td>Range Gram</td>
<td>Mean Gram</td>
</tr>
<tr>
<td>Euthyroxinemic *</td>
<td>31</td>
<td>3,226</td>
<td>2,580-4,791</td>
<td>450</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ 71.0</td>
<td>Range Gram</td>
<td>334-579</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.17</td>
<td>S.D. 5.39-10.15</td>
<td></td>
</tr>
<tr>
<td>Hypothyroxinemic adequate therapy II</td>
<td>11</td>
<td>3,222</td>
<td>2,500-3,997</td>
<td>450</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ 72.3</td>
<td>Range Gram</td>
<td>339-550</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.16</td>
<td>S.D. 5.37-9.10</td>
<td></td>
</tr>
<tr>
<td>Hypothyroxinemic inadequate therapy III</td>
<td>14</td>
<td>3,265</td>
<td>2,665-4,224</td>
<td>447</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ 131.8</td>
<td>Range Gram</td>
<td>273-794</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.84</td>
<td>S.D. 4.64-10.90</td>
<td></td>
</tr>
</tbody>
</table>

* Euthyroxinemic controls matched as to race, age, and gravida of mother and sex of child, and, if possible, by birth weight.

Reproduced by courtesy of C.V. Mosby Co., St. Louis, MO.

339 to 579 grams versus 273 to 794 grams for the inadequately treated hypothyroxinemic maternal-fetal pairs. Two of the placentas in this Group III weighed 616 and 794 grams and exceeded weights of the other 42 placentas. A low Leiter I.Q. of 76 was associated with a placenta markedly heavier (564 grams) than expected for a male infant with birth weight of 2,665 grams. Any significance of these heavy placentas is still unknown. Unfortunately, gross and microscopic examinations were not available for hypothyroxinemic pregnancies with poor outcomes of abortions, stillbirths, prematurity, and major anomalies.28(VI)

Three comments about the active metabolism of the placenta are pertinent. In Japan, chorionic villi from human placentas obtained by 12-week induced abortions deiodinated T4 as actively as villi from full term placentas.1 The authors concluded "feto-maternal exchange of T4 and T3 can be regulated by primary chorionic villi, even prior to completion of the placental organ, via deiodination of these compounds."1 Yoshida and Suzuki have written a series of articles about thyroid hormone concentrations in human placentas and have described activity of monodeiodinase.46 Emerson18(p31) wrote, "The placenta is usually regarded as a conduit through which maternal nutrients pass to the fetus, or as a barrier that allows for fetal development in an insulated environment . . ." ..."It is less recognized that the placenta is a metabolically active organ.”

Discussion

INCIDENCE OF MATERNAL HYPOTHYROXINEMIA IN PREGNANCY

How many women are hypothyroxinemic during the first trimester and unable to supply T4 to cross the placenta? Before the fetal thyroid assumes autonomous functions and when thyroid hormones are essential for early central nervous system development, maternal hypothyroxinemia could result in neurologic deficits of progeny.

Volpé in evaluation of the total population placed up to three percent in a
category of hypothyroidism.4(p275) "The presence of minor degrees of hypothyroidism (both mild and subclinical forms) will always be more common than the overt forms of the disease. The term will also embrace patients with 'compensated' hypothyroidism, i.e., normal circulating thyroid hormone levels with high thyroid stimulating hormones (TSH) values, as well as those with equivocal or slightly low thyroid hormone concentrations and elevated TSH levels.26 Up to three percent of the population can be placed in this category; it is much more common in females and has a much higher incidence with advanced age.35,89"4(p275)

Tunbridge made "Cross-sectional community surveys of non-iodine deficient Caucasian communities in England.41 Three percent of such a population proved to have biochemical evidence of minor degrees of thyroid failure as well as autoimmune thyroiditis." Interrelations of maternal and neonatal thyroid autoimmune disease to congenital hypothyroidism have not been clarified but are being investigated strenuously.2,16

Niswander34 published much quoted data that during pregnancy only 0.9 percent of 20,000 white women and 0.3 percent of 20,000 black patients in the Collaborative Project were hypothyroid. For these data, clinical diagnoses of hypothyroidism were required from about 14 medical centers with variant expertise in thyroidal diagnostics. Niswander himself admitted that those percents were undoubtedly falsely low. As a consultant, one of us (EBM) worked with the Collaborative Project at National Institutes of Health and recognized the defects of Niswander's data on thyroid diseases in pregnancy. Davies and Cobin12 emphasized that classical clinical symptoms of thyroid disease are masked in pregnancy. "A high degree of expertise strengthened by biochemical parameters with reference to the normal pregnant ranges have to be carefully evaluated before a therapeutic decision can be made."12

Gliner and associates21 reported in September, 1990, three percent hypothyroxinemia in Belgium in areas of marginally low iodine intake.26 Gliner et al21 and Burrow,3 in a covering editorial, admit that iodine intake was not extremely low but stress the intricacies of gestational thyroid function. Larsen and Mandel29 found in primary hypothyroidism a need for increased thyroxine therapy during pregnancy. Utiger, relative to therapy for hypothyroidism, wrote, "The fact that there are situations such as pregnancy and the postpartum period that necessitate alterations in dosage serves as a reminder of the multiplicity of extrathyroidal factors that can alter thyroid function."42(pl27) David Solomon wrote in a personal letter "I just do not know [the incidence of hypothyroxinemia in pregnancy]. The confounder is to what extent pregnancy increases demand and therefore brings out hypothyroxinemia in previously normothyroxinemic but hyper-TSH-emic women. This could bump it back to three percent. I just do not know the facts on that."*

At Providence Lying-In Hospital, Man looked for hyperthyroxinemia and was confounded by the high incidence of low BEIs. Standards for BEI were checked daily and cross checked with quantitative controls. In 1969, 173 of 1,394 clinic pregnancies were associated with low serum thyroxine-like iodines and/or clinical diagnoses of thyroid underfunction.28(v) This excessive percentage included many multigraviada and older women. At that point, any patient with every and/or any possible cause for a low serum thyroxine-like iodine was eliminated from the study. If a low BEI

* Personal communication to EBM.
occurred when a patient had a sudden weight gain or an upper respiratory infection,\(^{28(IV)}\) that low determination was classified as a sporadic false value. Only women with two authentic criteria of hypothyroxinemia were included. In 1976, Man and Serunian estimated that at least three percent of uncomplicated pregnancies in private and clinic practice at Providence Lying-In Hospital were hypothyroxinemic.\(^{28(IX)}\) Their data, Volpé’s the published report and letter by Volpe,\(^4\) community surveys by Tunbridge,\(^4\) the reference by Solomon* to “pregnancy’s increasing demands” support an incidence of three percent of hypothyroxinemia in otherwise uncomplicated pregnancies.

**VISUAL SPATIAL DISABILITIES**

The problem of maternal transfer of thyroxine through the placenta to the fetus pertains not only to the health of the mother and the fetus, but also to the future psychoneurological development of the progeny.\(^{14}\)

Unlooked for were low scores of some four-year-old progeny of hypothyroxinemic pregnant mothers adequately treated after 12 or 29 gestational weeks in gross motor tests of line walk and ball catch. Of these 17 children, three had strabismus, two wore glasses, and only 70 percent were classified “eyes normal” though 84 percent and 94 percent of the children in the other two groups were classified “eyes normal.” These hypothyroxinemic women had not registered at the prenatal clinic until 11 or 28 gestational weeks. Their hypothyroxinemia was neither recognized nor treated until 12 or 29 weeks. Adequate Proloid\(^\dagger\) had been prescribed and the serum BEIs of these mothers were in the normal range for pregnancy after 12 or 29 weeks.\(^{28(V)}\)

Irreversible brain damage and mental retardation of humans after prolonged thyroid failure during fetal and/or postnatal life have been emphasized by Delange in his discussions of fetal in utero thyroid failure.\(^{13}\) Many references to neurological deficits of hypothyroid children associate delayed bone age at birth with severe deficiency of thyroid hormones during early or prolonged fetal existence.\(^{14}\)

Both Farriaux of Lille, France\(^{19}\) and Van Vliet of Brussels\(^{43}\) found screening for congenital hypothyroidism effective in preventing mental retardation, but some children exhibited “mild abnormalities of perception and coordination at later ages.” Rochiccioli et al of Toulouse\(^{36}\) reported normal mental development of hypothyroid children discovered by screening and treated promptly, but in a minor degree neurological abnormalities were evident. The Catalan Collaborative Group in Barcelona\(^{23}\) also detailed certain ocular impairments, such as strabismus associated with fetal lack of thyroid hormones.

Not only in parts of Europe (France, Spain, Belgium, etc.) but also in North America these psychomotor and neuropsychological deficits of children have been found.\(^{15,16,22,37,38,33}\) At the 1989 Annual Meeting of The American Thyroid Association in San Francisco, a special satellite symposium was “Thyroid Hormone in the Developing Brain.” Joanne F. Rovet, Ph.D. (Toronto) spoke about “Neuropsychological Studies of Thyroid Hormone Deficiency in Humans—Windows on Early Brain Development.” Subsequently, she described hypothyroid children older than infancy but who had been diagnosed and treated and seemed to have mild intellectual impairments despite

* Personal communication to EBM.
\(^\dagger\) Donated generously by the Warner Lambert Co., Morris Plains, NJ.
normal IQs. These impairments occurred especially when intrauterine thyroid deficiencies were suspected.14

In Toronto, thyroid therapy for hypothyroid children was previously at a lower dosage than now used there and in New England. However, many at that 1988 conference in Brussels referred to psychomotor psychological deficits in children who, at birth, had delayed bone age and were thus suspected to have endured in utero thyroxine deficiencies.14

In contrast to some doctors in Toronto, Mitchell and Klein32,33 recommended higher doses of thyroid for hypothyroid infants. When tested at age nine to 10 years, 72 of these patients showed IQs which agreed well with those of their siblings and peers; however, several minor scores were noted, as in the reading comprehension subtotal of the Peabody Individual Achievement Test (PIAT) and the vocabulary subtest of the WISC-R. Delayed bone age at birth was reported for 53 of the 72 children, indicating perinatal hypothyroxinemia.

One of the first persons to advocate the testing of all newborns for hypothyroxinemia, which is now standard practice, was Dr. Man. Screening of thyroid function is urged in all pregnant women as well as testing prior to pregnancy in women who have experienced any difficulty in prior pregnancies. Our data indicate that there may be damage to the fetus when a pregnant woman has only a mild degree of hypothyroxinemia, even though she may appear clinically well. Hence screening is urged not only on newborns but also on pregnant women for hypothyroxinemia to prevent brain damage in newborns.

Addendum

After the paper was completed, Robert Z. Klein, M.D. wrote, "I would appreciate it if you would refer in your listed supports to the transplacental passage of thyroxine to my paper. The reference is Klein, R. Z.: In utero protection of the hypothyroid infant. In: Topics in Pediatrics. Pomerance, H. H. and Bercu, B. B., eds. New York, Springer Verlag, 1990, pp. 25–33."

References


