

Is Thyroid Inadequacy During Gestation a Risk Factor for Adverse Pregnancy and Developmental Outcomes?

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A workshop entitled, "The Impact of Maternal Thyroid Diseases on the Developing Fetus: Implications for Diagnosis, Treatment, and Screening," was held in Atlanta, Georgia, January 12–13, 2004. This paper reports on the individual session that examined thyroid inadequacy during gestation as a risk factor for adverse pregnancy and developmental outcomes. For this session the following papers were presented: "Adverse Pregnancy Outcomes"; "Thyroid Physiology in the Fetus"; "New England Data: Cretinism Revisited—Preventing Fetal Brain Damage when Mothers Have Subclinical Hypothyroidism"; "Dutch Data: Pregnancy, Maternal Thyroid (Dys)function and Outcome of the Offspring"; and "Report on the Wales Controlled Antenatal Thyroid Screening Study (CATS); A Prospective RCT." These presentations were formally discussed by invited respondents well as others in attendance. Salient points from this session about which there was agreement include the following. Maternal hypothyroidism is associated with complications of pregnancy and adverse effects on the fetus. These risks are greater in women with overt hypothyroidism compared to subclinical hypothyroidism, and also appear to be increased in women with euthyroid autoimmune thyroid disease. If maternal hypothyroidism is treated adequately, this appears to reduce the risk for adverse outcomes. The demonstration of a pattern of ontogeny of fetal cerebral cortex deiodinases and thyroid hormone receptors, beginning by 7–8 weeks' gestation, is circumstantial evidence that thyroid hormone plays an important role in fetal neurodevelopment. Significant fetal thyroid hormone production and secretion does not begin until approximately 20 weeks' gestation. If there is a significant role for thyroid hormone in fetal neurodevelopment before 20 weeks' gestation, it likely is of maternal origin. Studies demonstrate low levels of thyroxine in the fetal coelomic fluid and blood prior to 12–14 weeks' gestation. Published data consistently document a relationship between maternal thyroid deficiency during pregnancy and problems with neuropsychological development of the offspring.

Introduction

THIS REPORT, the fourth of six, contains the summaries of several papers presented to a workshop held in Atlanta, Georgia, January 12–13, 2004, to address "The Impact of Maternal Thyroid Diseases on the Developing Fetus: Implications for Diagnosis, Treatment, and Screening." The workshop was sponsored jointly by the National Center on Birth Defects and Developmental Disabilities, the National Center of Environmental Health, and the American Thyroid Association. The purpose of this individual session was to examine the evidence on thyroid dysfunction during pregnancy related to adverse fetal and child developmental outcomes. This session was organized and moderated by Drs. Stephen H. LaFranchi and James E. Haddow.

"Adverse Pregnancy Outcomes"

—Dr. Jorge H. Mestman

Dr. Mestman began his presentation with a review of previous studies linking maternal thyroid disease and adverse pregnancy outcome. The first large population study by Man and Jones ($n = 1420$) used a relatively crude evaluation of maternal thyroid function, measurement of butanol-extractable iodine (BEI) before pregnancy and after 24 weeks' gestation (1). By their definition, somewhere between 3% and 6% of pregnant women were hypothyroxinemic. Adverse outcomes, including preterm delivery (< 37 weeks' gestation), spontaneous abortion, stillbirth, and severe congenital malformations occurred in 19.6% of hypothyroid women compared to 12.2% of control women.

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Seven more recent series examined the frequency of adverse pregnancy outcomes in women with subclinical hypothyroidism (SCH) and overt hypothyroidism (OH) (2-8). The frequency of preterm birth averaged 6% in women with SCH and 20% in women with OH. The frequency of pregnancy-induced hypertension (PIH) averaged 11% with SCH and 23% with OH. The frequency of fetal death/perinatal mortality (PNM) was 2.9% in one study with SCH and averaged 7% with OH (Table 1).

Larger studies that included a control population do not always report statistically significant differences in these parameters. For example, Allan et al. (7), in a study of 209 hypothyroid women and 9194 controls, found that only fetal deaths were higher, 8.1% in women with a thyrotropin (TSH) greater than 10 mU/L, 2.9% in women with TSH 6-9.99 mU/L, and 0.9% in women with TSH less than 6 ($p < 0.001$). Gestational hypertension, vaginal bleeding, placental abrup-

tion, cesarean delivery, birth weight, and neonatal deaths were not different.

In another report with a control population, Leung et al. (5) found gestational hypertension and low birth weight to be increasingly higher their controls, women with SCH, and women with OH ($p < 0.02$) (see Table 1). They did not report a difference in maternal anemia, postpartum hemorrhage, fetal death, or congenital anomalies between SCH and OH women.

Wasserstrum and Anania (6) reported that women with severe hypothyroidism were more likely to undergo cesarean section for fetal distress as compared to mildly hypothyroid or euthyroid women (see Table 1).

Glinor et al. (9) reported spontaneous abortion in 3.3% of controls, 8% with a history of thyroid disorders, and 13.3% of women with autoimmune thyroid disease.

Autoimmune thyroid disease (AITD) also appears to be a risk factor for adverse pregnancy outcome. Studies by Stag-

TABLE 1. FREQUENCY OF VARIOUS ADVERSE PREGNANCY OUTCOMES IN WOMEN WITH SUBCLINICAL HYPOTHYROIDISM, OVERT HYPOTHYROIDISM, AUTOIMMUNE THYROID DISEASE, AND POSITIVE ANTITHYROID ANTIBODIES

	<i>p</i> =	<i>Control</i> %	<i>SCH</i> %	<i>OH</i> %	<i>AITD</i> %	<i>Ab+</i> %
General Complications of Pregnancy						
Man and Jones ^a (1)		12.2	19.6			
Preterm birth (Low birth weight)						
Davis (3)	NS			31		
Buckshee (4)	NS			15.4		
Leung (5)	2)	6.8	9	22		
Abalovich (8)	NS	11	7.2	20		
Glinor (11)	<0.005	8			16	
Deliveliotou (unpublished data)	NS	3.4	2.5	9.3	5.4 ^b	3.7
Casey (15)	0.03	2.5	4			
Pregnancy-induced hypertension						
Montoro (2)	NS			9		
Davis (3)	NS			44 ^c		
Buckshee (4)	NS			26.9		
Leung (5)	<0.02	7.6	15	22		
Allen (7)	NS	xxx ^d	xxx	xxx		
Glinor (11)	NS	xxx			xxx	
Zograbian (14)		3.8	7.7	11.6	12.7 ^b	14.8
Spontaneous abortion						
Abalovich (8)	NS	4	71.4 ^e	60 ^e		
Glinor (9)	<0.005	3.3			13.3	
Stagnaro-Green (10)	<0.011	8.4				17
Glinor (11)	<0.005	3.3			7	
Fetal death						
Montoro (2)	NS			9		
Davis (3)	NS			12		
Allan (7)	<0.001	0.9	2.9	8.1		
Perinatal mortality						
Buckshee (4)	NS			3.9		
Abalovich (8)	NS			3.2		
C-Section						
Montoro (2)	NS			22		
Wasserstrum & Anania (6)	<0.001		3	56		

^aSpontaneous abortion, stillbirth, congenital malformations.

^bThyroid disease on thyroxine.

^cPreclampsia.

^dxxx = thyroid status compared.

^eOvert hypothyroidism, inadequate treatment.

SCH, subclinical hypothyroidism; OH, overt hypothyroidism; AITD, autoimmune thyroid disease; Ab+, positive antithyroid antibodies.

naro-Green (10) and Glinoe et al. (11) reported that the rate of spontaneous abortion in women with positive antithyroid antibodies was double that of control women. Glinoe also found that preterm delivery was twice as common in women with AITD compared to their control population (11). A previous study from this group did not find a relationship between AITD and pregnancy-induced hypertension (12). In an autoimmune vein, in a study of 51 women with type 1 diabetes mellitus, Jovanovic-Peterson and Peterson (13) reported 8 (20%) developed clinical hypothyroidism and proteinuria during their pregnancy.

Dr. Mestman next reviewed personal studies carried out at USC-Los Angeles County Hospital and Clinics. Zograbian et al. (14) reported that both pregnancy-induced hypertension and prematurity were increased in women with a variety of treated and untreated thyroid disorders. They studied 143 women, including patients with SCH, OH, and euthyroid patients undergoing thyroid replacement therapy. Pregnancy-induced hypertension was increased most in patients with OH, and less so in women with SCH, compared to control women. It was also increased in euthyroid women undergoing thyroid replacement. The high frequency in this group may be explained in part by the high incidence of positive thyroid peroxidase (TPO) antibodies, almost 50%; in the half with positive antibodies, the frequency of pregnancy-induced hypertension was similar to the OH patients (Deliveliotou et al. unpublished data). Although prematurity appeared increased in babies delivered to women with OH, and less so in euthyroid women undergoing thyroxine therapy, this difference was not statistically significant. In the women hypothyroid at conception, those treated and euthyroid by 20 weeks' gestation had a lower overall pregnancy complication rate of 4.8%, whereas if they were treated and euthyroid after 20 weeks, the rate was 19%, and if they were never euthyroid, the rate rose to 31.5%. Dr. Mestman concluded that normalization of thyroid function early in pregnancy may reduce or prevent pregnancy-induced hypertension and its complications.

Discussant: Dr. Kenneth J. Leveno from the University of Texas Southwestern Medical Center reported pregnancy out-

comes in women with SCH. In their prospective study of 17,487 women screened 20 weeks' gestation or less, 2.3% met their criteria for SCH: TSH 97.5 percentile or more and free T₄ less than 0.68 ng/dL. Preterm birth, defined as gestational age 34 weeks or less at delivery, occurred in 4% of women with SCH compared to 2.5% of euthyroid women ($p = 0.03$). The risk for preterm birth persisted after adjustment for age and race (odds ratio [OR] 1.7, 95% [CI] 1.07–2.81) [Fig. 1; Courtesy of BM Casey et al. (15)].

Summary: Adverse Pregnancy Outcome: What Do We Know and What Do We Not Know?

—Dr. Stephen LaFranchi

What we know:

- Maternal hypothyroidism is associated with an increased risk of complications of pregnancy and adverse effects on the fetus. There appears to be a consensus that there is an increased risk of the following: (percentages from selected studies in parenthesis: control versus overt hypothyroidism):
 - Pregnancy-induced hypertension (3.8% → 11.6%)
 - Placental abruption
 - Spontaneous abortion (3.3% → 8%)
 - Fetal distress
 - Perinatal death (0.9% → 8.1%)
 - Preterm birth (3.4% → 9.3%)
 - Low birth weight (6.8% → 22%)
- The risk of these complications and adverse outcomes is greatest in women with overt hypothyroidism compared to SCH.
- Women with SCH appear to be at increased risk for some of the complications but not all studies show this.
- There also appears to be an increased risk of some adverse pregnancy outcomes in euthyroid women with AITD; these include:
 - Spontaneous abortion
 - Preterm birth
- Women with other autoimmune diseases are at risk for developing hypothyroidism during pregnancy; one study

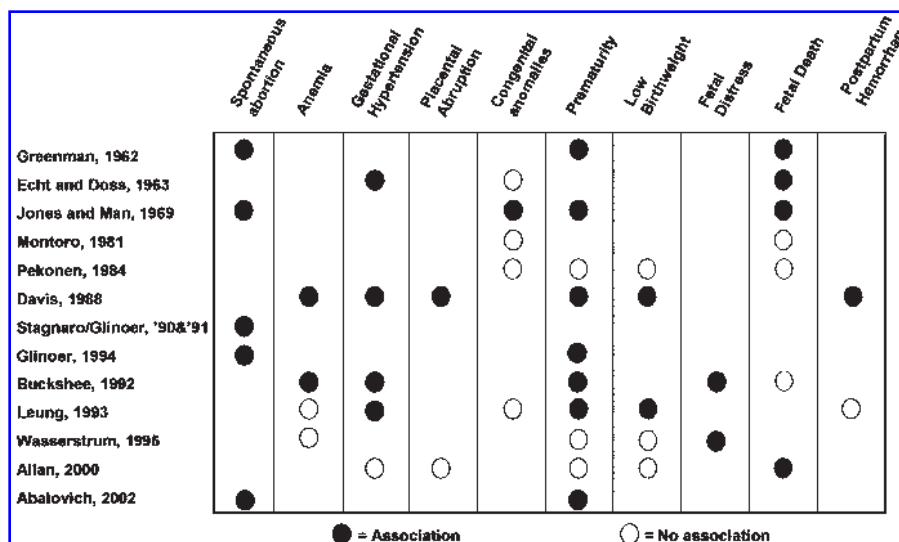


FIG. 1. The impact of maternal hypothyroidism on pregnancy. [Adapted from Casey (16)].

showed 20% of women with type 1 diabetes mellitus became hypothyroid during pregnancy.

6. If maternal hypothyroidism is treated early in pregnancy and women become euthyroid, this appears to reduce the risk for adverse outcomes.

What we do not know:

1. In women with SCH, whether adverse outcomes are clearly increased and to what degree.
2. In women with AITD, whether it is the maternal thyroid autoantibody itself or perhaps the reduced serum free thyroxine (FT₄) level that is associated with adverse pregnancy outcomes.
3. The ideal time to detect and treat maternal hypothyroidism to reduce or prevent adverse pregnancy outcomes; should this be preconception, or is early pregnancy sufficient?
4. Whether the untoward neurodevelopmental outcome in babies born to women with hypothyroidism is the result of reduced availability of maternal T₄ for transfer to the fetus or secondary to the adverse effects on pregnancy, or perhaps a combination of these factors.

“Thyroid Physiology in the Fetus”—Dr. Gabriella Morreale de Escobar

Dr. Morreale de Escobar began her talk by describing the different neurodevelopmental outcomes in babies born to mothers in areas of endemic iodine deficiency and in babies born with congenital hypothyroidism. Babies born to mothers with severe iodine deficiency are at risk for neurologic cretinism, resulting in mental retardation, deaf-mutism,

strabismic squint, and spastic diplegia. These babies will have completely normal thyroid function at birth if they receive adequate iodine. Conversely, babies born with congenital hypothyroidism are hypothyroid at birth and were presumed to be hypothyroid *in utero*. Yet the infants born to iodine-deficient mothers will have severe, irreversible brain damage caused by something that happened in the first half of pregnancy, whereas the infants born with congenital hypothyroidism, if detected and treated early, have a good neurodevelopmental outcome. To explain these differences, one needs to understand fetal thyroid development and the potential maternal thyroid contribution to the fetus, particularly in the first half of pregnancy before the fetus produces any significant thyroid hormone (Fig. 2) (16).

First Trimester

Fetal coelomic fluid and fetal serum thyroid hormone levels

Thyroid hormone present in the fetus in the first trimester, demonstrated in fetal coelomic fluid from 6 weeks’ and in fetal serum from 12 weeks’ gestation, are almost certainly of maternal origin. Contempre et al. (17), from Dr. Morreale de Escobar’s group, demonstrated that T₄ levels in the coelomic cavity as early as 6 weeks’ gestation were approximately 1/100 of the maternal level, and rose to 0.7 μg/dL (9.0 nmol/L) by 11 weeks. The concentrations of coelomic fluid T₄ paralleled the rise in maternal serum T₄. Further studies by Calvo et al. (18), also from Dr. Morreale de Escobar’s group, reported that FT₄ levels were closer to maternal levels, because of low thyroxine-binding globulin (TGB) and other binding proteins. Fetal coelomic fluid FT₄ rose from

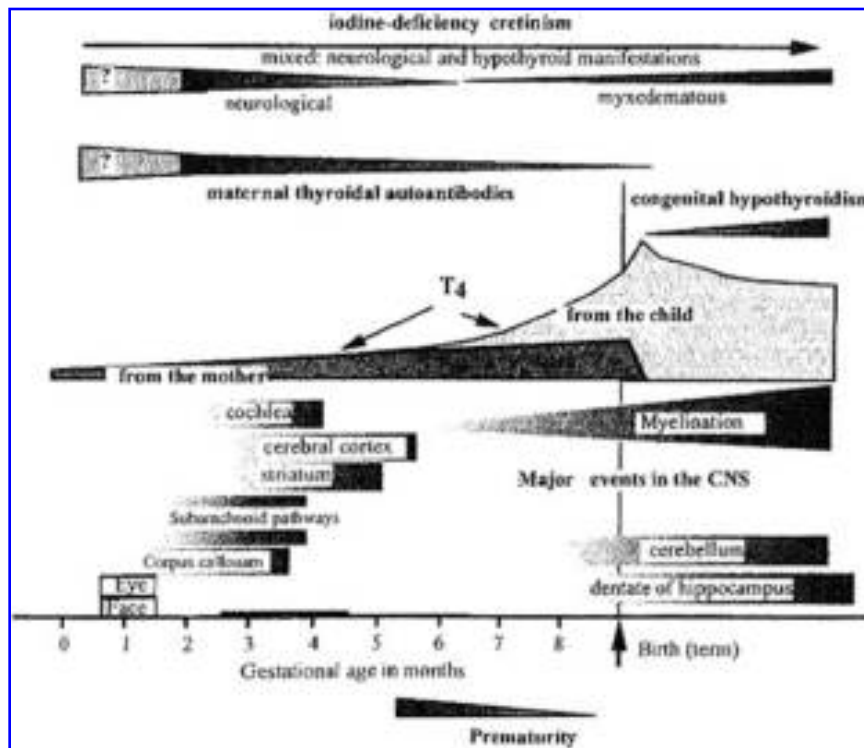


FIG. 2. Approximate timing for major insults to the brain resulting from hypothyroxinemia, superimposed on major neurodevelopmental events. Conditions resulting in early maternal hypothyroxinemia, combined with later impairment of the fetal thyroid, are the most damaging, with central nervous system injury that is irreversible at birth. [Adapted from Morreale de Escobar (16)].

approximately 0.15 ng/dL (1.9 pmol/L) at 6 weeks to 0.45 ng/dL (5.8 pmol/L) at 11 weeks. Fetal coelomic T₃ remained low, approximately 2 ng/dL (0.04 nmol/L).

By 12–14 weeks' gestation, Calvo et al. were able to measure fetal serum thyroid hormone levels. From 12–14 weeks to 18 weeks, fetal serum T₄ rose from 0.3 to 1.2 μg/dL (4 to 16 nmol/L); FT₄ rose from 0.3 to 0.6 ng/dL (4 to 8 pmol/L); T₃ remained low at approximately 32 ng/dL (0.5 nmol/L), and TSH ranged from 2.9 to 7.2 mU/L.

Dr. Morreale de Escobar's group concluded that fetal fluids and serum have very low ontogenically determined concentrations of thyroid hormone-binding proteins; these protein levels are independent of maternal thyroid status. Most of the maternal T₄ and T₃ that reaches these compartments before midgestation are in the "free" form and so levels reach biologically significant amounts. As described below, they believe there is evidence that these maternal hormones play an important role in fetal development, particularly of the nervous system. At the same time, they make the point that the placental "barrier" is necessary to prevent free T₄ and especially T₃ from reaching fetal tissues at levels that likely would prove harmful.

Fetal iodothyronine deiodinases

There is evidence that the developing brain depends on circulating T₄ that is locally deiodinated to T₃. Iodothyronine deiodinases regulate systemic levels of T₃ and local delivery of T₃ to thyroid nuclear receptors. This is carried out primarily by type 2 or 5'-deiodinase (5'-D2), the main deiodinase in the brain and pituitary. Type 1 or 5'-deiodinase (5'-D1) that is present in liver, kidney, and other tissues and is more important for systemic conversion of T₄ to T₃, is not present in the fetal brain. 5-Deiodinase (5-D3) that deiodinates both T₄ and T₃ to metabolites devoid of thyroid hormone-like activity, already plays a very important role in the human brain before midgestation. The ontogeny of deiodinases in the fetal cerebral cortex in the first trimester might lend support for a role of maternal thyroid hormone in fetal neurodevelopment.

In an investigation carried out in the human fetus, Chan et al. (19) reported that iodothyronine deiodinase mRNAs were expressed in the cerebral cortex from 7–8 weeks' gestation. The relative 5'-D2 mRNA expression was similar to the adult cerebral cortex at 7–8 weeks, with a rise at 15–16 weeks above adult levels. The 5'-D2 enzyme activity (determined by release of specific radioactive iodothyronines), although variable, exceeded adult levels at 7–8 weeks and then decreased to adult levels by 17–20 weeks. The relative 5'-D1 mRNA expression was variable, rising above adult levels between 11 and 16 weeks. However, the 5'-D1 enzyme activity was below the level of detection between 7 and 20 weeks' gestation. 5-D3 mRNA expression was present from 7–8 weeks in the fetal cerebral cortex, but reduced in comparison to adult brain. However, 5-D3 enzyme activity was greater in the fetal cerebral cortex compared to the adult brain (as described below, its main activity is in the placenta). In summary, Chan et al. (19) found a pattern of deiodinase mRNA expression and activity in the fetal cerebral cortex beginning at 7–8 weeks' gestation and varying for each subtype.

Fetal brain thyroid hormone receptors and thyroid occupancy

In a similar vein, investigations of the ontogeny of thyroid hormone receptor isoforms in the fetal cerebral cortex lend support for a role for thyroid hormone in the first trimester. Thyroid hormone receptor (TR) mRNA expression for TR_{α1}, TR_{α2}, and TR_{β1} were present from 7–8 weeks' gestation (19,20). TR_{β2} mRNA expression was absent from the majority of samples. TR_{α1} and TR_{α2} mRNA expression appeared to increase from 8 to 14 weeks' gestation (19). At several time periods between 7 and 20 weeks, TR_{α1} mRNA expression was higher in the fetal cerebral cortex compared to the adult. The expression of TR_{α2} and TR_{β1} mRNA, though present, was generally lower than in the adult brain (18). Earlier studies by Bernal et al. (21), that show that brain nuclear TRs are partially occupied by T₃ at 9–10 weeks' gestation, are further evidence for a role of maternal thyroid hormone. These studies looked at the cerebral cortex as a whole; the investigators commented that different anatomical areas of the brain need to be studied, as they are likely to have different deiodinase and TR activities.

Second and Third Trimester

Serum thyroid hormone levels

Fetal thyroid hormone secretion begins around 18 to 20 weeks' gestation, coinciding with full development of the pituitary-portal vascular system. In samples obtained by cordocentesis, that is, without interruption of maternal-fetal vascular connections, fetal serum T₄ rises from a mean of approximately 2 μg/dL (26 nmol/L) at 12 weeks to 10 μg/dL (138 nmol/L) at term (22). The rise in serum T₄ is caused by both to an increase in hepatic production of serum TBG, and to a lesser degree to fetal thyroidal T₄ production under TSH stimulation. Fetal serum FT₄ levels increase progressively, from a mean of approximately 0.1 ng/dL (1.3 pmol/L) at 12 weeks to 2.0 ng/dL (25.7 pmol/L) at term. Because of the activity of placental type 3 or 5-deiodinase 3 (5-D3), which converts T₄ to reverse triiodothyronine (rT₃) and T₃ to reverse T₂, fetal serum total and free T₃ levels show a much smaller increase. Fetal serum T₃ levels rise from approximately 6 ng/dL (0.09 nmol/L) at 12 weeks to 45 ng/dL (0.68 nmol/L) at term. Serum TSH levels rise gradually from approximately 4 mU/L at 12 weeks to 8 mU/L at term; they are always higher than in the maternal circulation and adult values of euthyroid persons. The origin and developmental role of this fetal TSH is not well understood. Maturation of the hypothalamic-pituitary-thyroid axis and negative feedback does not appear to be complete until a few months after birth, with intrauterine levels of free T₄ and TSH being positively correlated up to birth. The intrauterine FT₄ levels are significantly higher than those found in age-paired premature infants (23,24), leading to the conclusion that maternal transfer of T₄ continues to contribute significantly to the hormone available to fetal tissues.

Fetal brain thyroid hormone content

Studies from Dr. Morreale de Escobar's group have examined the concentrations of T₄, T₃, and rT₃ in the fetal cerebral cortex and cerebellum between 13 and 20 weeks'

gestation. The cerebral cortex showed a rise in T_4 , an even greater rise in T_3 , and a fall in rT_3 (25). These findings indirectly support a role for elevated levels of 5'-D2 that converts T_4 to T_3 in the cortex, and conversely low levels of 5-D3. In contrast, in the cerebellum T_3 levels remained low over the 13- to 20-week period; T_3 rises later, between 30 weeks and term. These findings suggest 5'-D2 activity is low and 5-D3 is high in the 13- to 20-week period; T_3 concentrations rise toward the end of pregnancy as 5-D3 activity falls. Other regions of the brain (midbrain, basal ganglia, brain stem, spinal cord, hippocampus) showed a similar pattern with low T_3 concentrations until 5-D3 started to decrease around midgestation. The investigators concluded that the thyroid hormone concentrations follow different patterns in different brain areas. 5-D3 activity appears to limit exposure to systemic and locally produced T_3 , allowing for cell growth, until higher T_3 concentrations are required for cell differentiation (25).

Based on the above summary, it seems clear that if thyroid hormone plays any role in fetal development in the first third to half of gestation, it must be of maternal origin. In the 1970s and 1980s, investigations of maternal thyroid hormone transfer, carried out primarily in sheep, concluded that there was no significant transfer of T_4 or T_3 to the fetus. This uterine-placental "barrier" was caused, in large part, to the placental 5-D3 described above. Then a report by Vulsmas et al. (26), in 1989 in infants with total organification defects and agenesis, such that they were unable to produce any T_4 , showed that cord T_4 levels ranged from 2.7–5.5 $\mu\text{g}/\text{dL}$ (35–70 nmol/L), demonstrating that approximately one third of maternal T_4 crossed to the fetus at term. These levels are likely sufficient to protect the fetal brain in infants with congenital hypothyroidism. If such infants are detected by newborn screening programs and treatment started early enough, their neurologic outcome is good.

Animal Experiments

In experimental animal models using iodine-deficient rat dams and fetuses, maternal hypothyroidism results in abnormal neuronal cell migration in the somato-sensory cortex and hippocampus (27). There are decreased cells in the superficial layers and increased cells in the deeper layers, blurring of cell layers, and heterotopic cells. Overall, this results in abnormal brain cytoarchitecture (28). A more recent experimental animal model has shown that even a relatively minor and transient degree of maternal thyroid hormone insufficiency during a specific developmental window results in the same irreversible abnormalities in the brain of the progeny, that can only be prevented by treating the dams with T_4 (29).

Thus, one could postulate that maternal hypothyroxinemia would result in reduced transfer of T_4 to the fetus with potentially harmful effects on fetal neurodevelopment (30). This is clearly the case in areas of endemic iodine deficiency, where infants born to iodine-deficient mothers suffer neurologic cretinism. In this situation, both the mother and fetus may be hypothyroxinemic. The evidence for an effect of maternal hypothyroxinemia alone on fetal neurodevelopment based on human epidemiologic studies will be presented in the next section.

Summary of Session 3: Thyroid Physiology in the Fetus. What Do We Know and What Do We Not Know?—Dr. Stephen LaFranchi

What we know:

- The demonstration of a pattern of ontogeny of fetal cerebral cortex deiodinases and thyroid hormone receptors, beginning by 7–8 weeks' gestation, is circumstantial evidence that thyroid hormone plays an important role in fetal neurodevelopment.
 - Deiodinases
 - Type 1 or 5'-deiodinase (5'-D1): not present in fetal brain
 - Type 2 or 5'-deiodinase (5'-D2): mRNA measurable by 7–8 weeks; activity similar to adult brain; increased with hypothyroidism
 - Type 3 or 5-deiodinase (5-D3): mRNA measurable by 12–14 weeks; activity > adult brain (also in placenta; "protective" of too high transfer of T_4)
 - Thyroid hormone receptors (TR)
 - $\text{TR}\alpha_1$, $\text{TR}\alpha_2$, and $\text{TR}\beta_1$ mRNA present from 7–8 weeks' gestation in fetal brain
 - $\text{TR}\beta_2$ absent in fetal brain
 - Cerebral cortex rise in $T_4 > T_3$, and fall in rT_3 between 13 and 20 weeks' gestation
 - Cerebellum T_3 remains low over 13 to 20 weeks', but rises after 30 weeks' gestation
- Significant fetal thyroid hormone production and secretion does not begin until approximately 20 weeks' gestation.
- Fetal serum T_4 rises from 20 weeks to term (2 → 10 $\mu\text{g}/\text{dL}$); T_3 levels relatively much lower (6 → 45 ng/dL). TSH shows a small rise to term (4 → 8 mU/L); hypothalamic-pituitary-thyroid axis not mature until a few months after delivery.
- T_4 demonstrated in the fetal coelomic cavity as early as 6 weeks' gestation.
- The concentration of coelomic fluid T_4 correlates positively with maternal serum T_4 levels.
- FT_4 concentrations are closer to maternal FT_4 levels, because of low TBG and other binding proteins in the fetus. Coelomic fluid FT_4 rises from 6 to 11 weeks (0.15 → 0.45 ng/dL); fetal serum FT_4 rises from 12 to 18 weeks (0.3 → 0.6 ng/dL).
- If there is a significant role for thyroid hormone in fetal neurodevelopment before 20 weeks' gestation, it likely is of maternal origin.
- Based on cord T_4 levels in infants with total organification defects or agenesis, approximately one third of maternal T_4 crosses to the fetus at term.

What we do not know

- How much maternal T_4 crosses to the fetus in the first and second trimester.
- Of the fetal serum T_4 levels measured at 12 weeks to term, how much is fetal and how much is maternal in origin.
- How the ontogeny of deiodinases and thyroid hormone receptors differs in different anatomic regions of the fetal brain.
- Whether there are critical developmental "windows" that may result in irreversible brain damage with hypothyroxinemia, even if corrected later in pregnancy.

- At what period during pregnancy treatment of transient maternal hypothyroxinemia, whether from iodine deficiency or autoimmune thyroid disease, can reverse the effects of maternal hypothyroidism.

“New England Data: Cretinism Revisited—Preventing Fetal Brain Damage when Mothers have Subclinical Hypothyroidism”—Dr. Robert Z. Klein

Iodine prophylaxis for maternal endemic hypothyroidism has been known to eliminate cretinism since the first half of the twentieth century. More recently, iodine replacement was recognized as an effective treatment starting as late as the end of the first trimester (31). The fetal brain damage of cretinism resulting from maternal autoimmune hypothyroidism first described in 1960 was shown to be prevented by prophylactic T₄ in 1990 (32,33). The brain damage of milder clinical and subclinical maternal hypothyroidism was reported in 1971 to be prevented by administration of T₄ at unspecified times during gestation (34). Our validation of this work was reported in 1999 (35) and summarized in three other publications (36–38). In two preliminary prospective studies, we established that almost 2.3% of 12,000 women had TSH values 6 mU/L or more (0.3% of the values were 12 mU/L or more) at 17 weeks' gestation. The combined rate of stillbirths, spontaneous abortions, and intrauterine deaths after 17 weeks' gestation was almost 6 times greater among women with TSH concentrations 6 mU/L or more than among control mothers ($p < 0.013$).

Our third study examined the relationship between maternal TSH levels during pregnancy and IQ of offspring at age 8 years (35). TSH measurements were performed on serum samples obtained from 25,000 women during the seventeenth week of gestation and stored at -20°C for 8 years. Three groups of mothers and their children were selected for further study from within this cohort (group 1). Fourteen hypothyroid mothers who were treated before and during pregnancy (group 2). Forty-eight mothers with subclinical autoimmune hypothyroidism diagnosed only after screening the stored sera; and group 3, 124 controls. TSH levels for groups 1 and 2 were 97.7th percentile or more. For group 3, TSH levels were less than 97th percentile. Mean full-scale WISC IQs for these groups were 111 ± 13 ; 100 ± 16.3 ; and 107 ± 13 , respectively. More than twice as many children of untreated hypothyroid mothers (group 2) had an IQ more than 1 standard deviation (SD) below the control (group 3) mean, and four times as many had IQs more than 2 SDs below the control mean. In spite of elevated TSH measurements in group 1 women (treated), the average IQ of offspring was *not* lower than controls. We inferred that their thyroid hormone levels had been adequate was present earlier in gestation, when the need might have been greatest. Maternal TSH, FT₄, and thyroglobulin (Tg) all correlated univariately with children's IQ, but only TSH correlated significantly in multivariate analyses (37). In iodine-deficient regions, elevated Tg concentrations are more sensitive indices of perturbations of thyroid function than are FT₄ and TSH (16). In our study, Tg levels were shifted into a higher range only among the 62 women with elevated TSH levels, compared to both the 124 control women and 100 nonpregnant control women. Similarly, FT₄ levels were shifted lower only among the 62 women with high TSH levels, again in comparison to

both control groups. This indicates that Tg measurements are not likely to add useful information as part of a screening panel in iodine-sufficient areas.

Using our data, we calculated that more than 11 children with IQ measurements of 1 or more SDs below the mean can be attributed to maternal hypothyroidism for every 10,000 children. This would total 4600 children affected per year in the United States. For comparison, the number with low IQ associated with congenital hypothyroidism before the advent of newborn screening was 1 per 10,000. Children born to mothers with subclinical hypothyroidism comprise a minimum of 0.8% of all children with IQs more than 1 SD below the mean and 1.5% of all children with IQs more than 2 SDs below the mean (over 1400 per year in the United States).

There are few data indicating when mothers with autoimmune hypothyroidism must be treated to prevent fetal brain damage. Dr. Klein stated that parsimony would suggest it would be the same as in endemic hypothyroidism, but this can be determined by correlating the IQ of children of treated mothers with the gestational age at which treatment was begun. In one study, eight mothers were diagnosed and treated at 5 to 10 weeks' gestation. All of the children had normal IQs at 4 to 10 years of age (39). In another study, one woman with overt and eight women with subclinical autoimmune hypothyroidism were similarly treated. Their children's development was normal at age 10 months (40). These data, while encouraging, are obviously insufficient. Filling gaps in our knowledge requires studies of larger numbers of mothers and their offspring; however, the answers from current studies should be forthcoming within 5 years if sufficient numbers can be recruited in the first 8 to 10 weeks of gestation.

Meanwhile Dr. Klein proposed that it should be a public policy to educate women to seek obstetrical care as soon as they miss a menstrual period. They would be screened for hypothyroidism with TSH and FT₄ measurements. Pending laboratory results, all mothers would be treated with T₄ as early as possible. This would be continued throughout pregnancy if TSH was greater than 97.7th percentile or FT₄ was less than the 2.3th percentile. Fortunately, sensitive thyroid feedback mechanisms prevent nonintentional over dosage of T₄ unless the subject has subclinical *hyper*thyroidism. Mothers would be monitored regularly and their thyroxine dose adjusted to maintain TSH below and FT₄ above their respective medians. This would prevent the possible brain damage of 23,000 fetuses in the United States during the 5 years while awaiting the results of a definitive study.

Because much more information is needed to develop a national policy, it is important that several options be discussed and implemented for identifying and treating pregnant or nonpregnant women of child bearing age to learn the best manner of identifying those at risk and their treatment.

Dr. James E. Haddow

What we know:

- Published data consistently document a relationship between maternal thyroid deficiency during pregnancy and problems with neuropsychological development of the offspring.

- Such problems can occur even with milder degrees of thyroid deficiency.
- In the population-based study described above, full scale WISC IQs averaged 7 points lower among children born to mothers with undiagnosed thyroid deficiency during pregnancy, in comparison with matched control children.
- More than twice as many of these children had IQ measurements more than 1 SD below the control mean, and four times as many had IQs more than 2 SDs below.
- From these data, it is possible to extrapolate that IQ measurements below 1 SD might be avoided in 4600 children annually in the United States, if diagnosis and treatment of their mothers were completely effective.
- Iodine deficiency appears not to be a factor in producing maternal thyroid deficiency in the study population described above, as inferred from Tg measurements.

What we do not know:

- Only fragmentary data exist to indicate that thyroid replacement beginning early in pregnancy will reduce or avoid problems with fetal development.
- Further studies are necessary to identify the optimal approach to diagnosis and treatment and to document efficacy.

“Dutch Data: Pregnancy, Maternal Thyroid (Dys)function and Outcome of the Offspring” —Dr. Victor J. Pop

In the beginning of the 1990s we found a significant relation between postpartum depression and postpartum thyroid dysfunction in a sample of 298 pregnant women in the general population (41). A follow-up study by us in 225 of these women in 1995 demonstrated a 10-point IQ delay among 5-year-old children of the 19 women with thyroid peroxidase (TPO) antibodies at 32 weeks' gestation. The control group was children of the 206 women without TPO antibodies at 32 weeks' gestation (42). In reviewing this 1995 data set for the present meeting, I found that IQ (McCarthy) scores averaged seven points lower among 5-year-old children of the 22 women with FT₄ levels at or below the 10th percentile at 32 weeks' gestation. The control group was children of the remaining 203 women. Maternal TSH levels above the 95th centile were not associated with lower IQ.

We then began a second study involving 300 women to assess thyroid function at 12 and 32 weeks' gestation. That study showed that psychomotor development at age 10 months was impaired among children whose mothers' FT₄ values were less than the 10th percentile at 12 weeks' gestation. No developmental delays were found in association with either low FT₄ values or TPO antibodies at 32 weeks' gestation (43).

In our third, larger study, 1361 women's FT₄ and TSH levels were measured at 12 weeks' gestation, and a subset of 125 cases (FT₄ < 10th centile) and 125 controls (FT₄ 50th to 90th centile), was identified for repeat measurements at 24 and 32 weeks' gestation, along with follow-up of children (44). After exclusion of several women with abnormal TSH during gestation, mental and psychomotor development index scores at 2 years of age averaged eight points lower among 57 children of the mothers whose FT₄ levels were be-

low the 10th centile, in comparison to scores of 58 control children. Among the control mothers, lower FT₄ levels at 24 and 32 weeks' gestation were not related to lower IQ scores.

I now show some new data from this study. All newborns in Holland are screened for hypothyroidism between the fourth and seventh day, using total T₄. We find no relationship between 205 mothers' FT₄ levels at 12 weeks' gestation and total T₄ levels of their newborns, but, at 32 weeks' gestation, maternal T₄ levels above the 90th centile are associated with lower neonatal total T₄ levels. All of these children are euthyroid. We then analyzed Bayley scores from 157 of these children at 1 and 2 years of age. Psychomotor development index scores were lower at age 1, but not at age 2 among the 23 infants with total T₄ concentrations 1 SD or more below the mean. The mental development index scores were not different at either age. We also have looked at obstetrical outcome among 98 women in this study with FT₄ values the 10th centile or less at 12 weeks' gestation in comparison to 104 women with FT₄ values between the 50th and 90th centiles. Fetal breech position at term occurred in 10 of the former group versus two of the latter (relative risk [RR] 4.7, 95% CI: 1.2–19) (45).

Our fourth study is underway. It involves 1500 women who will all be followed at 12, 24, and 36 weeks' gestation, assessing the same thyroid parameters as in our third study, except that urinary iodine is also to be measured; infant development is to be assessed at 2 and 5 years in a subset of this sample. Preliminary results from 504 women show the expected pattern of TPO measurements (becoming lower as gestation advances) and a 2.2% rate of subclinical hypothyroidism. The expected relationship between TSH and FT₄ is seen at 12 weeks' gestation, but not at 24 or 34 weeks' gestation.

Based on the work summarized in this presentation, I conclude that low maternal T₄ rather than TSH concentrations during gestation in euthyroid women is related to impaired infant development up to 5 years of age. [Note: this finding is for low FT₄ at 12 weeks' gestation up to age 2 in one cohort, and for low FT₄ at 32 weeks' gestation up to age 5 in a second cohort]. Preliminary data show that high levels of FT₄ in euthyroid women late in gestation are associated with lower levels of their newborns' total T₄ levels. This needs to be explored further, including the implications.

Dr. James E. Haddow

What we know:

- The main, published study described above focuses on children of euthyroid mothers (as defined by TSH levels that are not elevated).
- The maternal FT₄ level at 12 weeks' gestation is the variable being examined in relation to the offspring's neurodevelopmental performance.
- At 2 years of age, mental and psychomotor index scores average 8 points lower among children of mothers whose FT₄ levels were below the 10th centile, in comparison to controls.
- From an earlier data set, we have discovered retrospectively that a similar relationship exists, when the mother's FT₄ level is below the 10th centile at 32 weeks' gestation.

5. Unpublished data from our main study indicate that higher maternal FT₄ levels at 32 weeks' gestation are associated with lower neonatal T₄ levels, but that lower neonatal T₄ levels among euthyroid children are not associated with adverse developmental consequences.

What we do not know:

1. It is not yet known whether these developmental problems persist into later childhood and beyond.
2. Only fragmentary data exist to indicate that thyroid replacement beginning early in pregnancy will reduce or avoid problems with fetal development.
3. Further studies are necessary to identify the optimal approach to diagnosis and treatment and to document efficacy.

“Report on the Wales Controlled Antenatal Thyroid Screening Study (CATS); A Prospective RCT —Dr. John H. Lazarus

The CATS study was begun to determine if thyroid function screening in early gestation is justified. In the United Kingdom, nearly all pregnant women attend a booking clinic at around 13 to 16 weeks' gestation. Sera are to be collected from 22,000 women with singleton pregnancies at less than 16 weeks' gestation, who are randomly assigned to one of two groups. The screened group will have T₄ and TSH tested. Women with the highest 2.5 percentile of TSH or the lower 2.5 percentile of T₄ are given treatment with 0.15 mg of T₄ daily. The other sera group remains untested until the women deliver, when the sera are measured for T₄ and TSH in the same laboratory. Abnormal levels are reported at that time to the physician, and the woman is placed on treatment as indicated. All children will have developmental testing at age 2 years and again at age 5 years.

The trial is adequately powered to detect a difference at least at the 80% level. As of October 31, 2003, 5270 women were enrolled. Of that group, we found abnormal thyroid function tests of 108 individuals. Approximately 45% had high TSH and normal FT₄, 52% had low FT₄ with normal TSH, and 3% had both high TSH and low FT₄.

The data on the unscreened group were very preliminary because many women have not yet delivered. The numbers are very small, but similar outcomes emerged of a high TSH group and a low T₄ group with very little overlap. Preliminary data on thyroid hormone concentrations at recruitment showed no significant difference between low FT₄, or a T₄ to T₃ ratio, and a normal TSH in the low FT₄ group. When antibodies were tested, more than 50% of the high TSH group had positive TPO antibodies, versus only approximately 10% in the low T₄ group. The latter parallels the measurements by studies of postpartum disease in the normal population of pregnant women.

The study measured urinary iodine in a random spot sample of 164 women. The median urinary iodine was 100 μg/L (range, 11–480 μg/L). The United Kingdom is supposed to be iodine-sufficient; however, these studies seem to provide some evidence of iodine deficiency. Two other as-yet unpublished studies suggesting this were shared. It would be interesting to determine whether the iodine deficiency re-

sides in the low T₄ group, the high TSH group, or perhaps is equally spread with the controls.

Study enrollment is now at approximately 6000, apparently comprised of 3.3% or 3.5% with subclinical hypothyroidism. With that percentage, total enrollment can probably be lowered to 15,000, which is fortunate since recruitment has been slow to date. Other challenges include budget, the reluctance of a minority of family physicians to prescribe levothyroxine (LT₄) to the women identified as being hypothyroid, and study length, because the last developmental test will be done when the children are 5 years old.

Discussion included:

Dr. Robert C. Smallridge: *Many of the treated study women have TSHs of 4.0–4.5. Will there be follow-up on their TSHs during pregnancy, since 150 μg of T₄ could suppress TSH and risk overtreatment?*

Understood, but the normal TSH levels in pregnancy are unclear; many think it drops as does FT₄. Monitoring is being done. The women start T₄ just before 16 weeks and have another blood test 6 weeks later and then at 30 weeks. Of the first 100, one woman's dose was lowered as a precaution by 25 μg; two or three other dose regimens were increased.

How will the number of people who are iodine deficient affect the statistical analysis, since that introduces another variable?

It will not affect the trial's original aim or the intention-to-treat analysis, but it will be a consideration in the subgroup analysis. But this study approach is from a pragmatic, health service point of view. Cost effectiveness will be a factor, and may add to the proposal of adding iodine supplementation as was done for folic acid.

Dr. Joanne Rovet: *Is 16 weeks late to start treatment to affect fetal outcomes?*

Yes. A screening program to begin 2 weeks after the missed period, or even a preconception clinic for targeted focus groups, as done for type I diabetes, is biologically desirable. If a universal screening strategy is not adopted, the latter may be second best. But other factors require care in introducing screening, such as balancing the woman's anxiety from screening with the benefits.

Discussant: Dr. Joanne Rovet reemphasized the points made earlier by Dr. Morreale de Escobar, namely, that T₄ is essential for human brain development. Studies with animals show that the timing of need for TH varies within the brain. The retina, corpus callosum, thalamus, cochlea and striatum are most in need of T₄ in the first half of pregnancy, whereas much of the cortex, cerebellum and hippocampus need T₄ later during gestation or postnatally. Within the hippocampus itself, different substructures also appear to develop at different rates and so may have different timing of need for T₄.

In her presentation of the “Visual Development in Offspring of Women with Treated Hypothyroidism during

TABLE 2. A REASONABLE PSYCHOLOGICAL TEST BATTERY—INFANT

<i>Construct</i>	<i>Structured context</i>	<i>Natural environment</i>
Cognitive development Motor development	Bayley Scales of Infant Development Bayley Scales of Infant Development	
Adaptive behavior skills Language development	Preschool Language Scale	Vineland Adaptive Behavior Scales Receptive-Expressive Emergent Language Scale
Temperament		Infant Behavior Questionnaire

Pregnancy," she pointed out that the above neural structures subserve different specific abilities and that a lack of T₄ during pregnancy can disrupt the normal development of a variety of skills, the nature of which depends on the timing of T₄ insufficiency.

While the studies of outcome after maternal hypothyroidism, which were just presented, have shown suboptimal outcome in the offspring, those studies either evaluated only global abilities in infants (i.e., Pop) or not the full spectrum of affected abilities (i.e., Haddow). It is also important to note that in the work on infants (Pop), infant neurodevelopment tests have low predictability for subsequent intellectual functioning. In the Haddow study, which assessed older children comprehensively, the only prenatal measurement was TSH at 16 weeks' gestation and memory was not studied. Furthermore, while there were reports of normal functioning in children whose mothers received treatment, these children still had persisting attention deficits.

From her research in Toronto, using techniques to measure visual and attention abilities and specific memory functions that would be particularly vulnerable to maternal hypothyroidism and later tests of visual contrast sensitivity and visual acuity in infancy, she was able to correlate child outcome with results of maternal thyroid function tests at each of the three trimesters of pregnancy. In the first two trimesters of pregnancy, higher maternal TSH or lower ma-

ternal FT₄ were associated with weaker infant memory and visuomotor skills, reduced contrast sensitivity in infancy, and poor visual attention at age 5. Higher maternal TSH in the third trimester was associated with increased distractibility and shorter processing times on infant attention tests and lower full scale IQ and weaker memory and attention skills (namely, more impulsive responding) at age 5.

Deficits were observed in basic low-level visual abilities, sensorimotor abilities, and memory skills although the maternal hypothyroid group did not differ from controls on indices of global cognitive ability or school functioning. Therefore this research suggests that the effects on different abilities reflect timing of the lack of T₄ with the retina and subcortical structures appearing to be T₄-dependent early in pregnancy whereas cortical structures, with a posterior-to-anterior gradient, need TH later in pregnancy or beyond.

Discussant Dr. Susan Waisbren: As a follow-up to data just shown about the relationship between maternal thyroid deficiency and the child's neuropsychological development, my comments are largely directed at the implications of low IQ, from a learning, social, and societal perspective. I also will show examples of reasonable panels of tests to be used at different ages, and recommend that an attempt be made by investigators to use common panels, for ease of comparison. In general, the purpose of testing in this type of research setting is to identify developmental delay, examine skill dis-

TABLE 3. A REASONABLE PSYCHOLOGICAL TEST BATTERY—CHILD

<i>Construct</i>	<i>Structured context</i>	<i>Natural environment</i>
Cognitive development Neuropsychological functioning	Stanford-Binet Intelligence Scale NEPSY; California Verbal Learning Test	Behavior Rating Inventory of Executive Functions
Academic skills	Woodcock-Johnson Test of Achievement	
Adaptive behavior skills Emotional/behavioral functioning		Vineland Adaptive Behavior Scales Behavior Assessment System for Children

crepancies, and disentangle environment and biological/genetic effects. For children in the early years (through age 3 years) the Bayley Scales of Infant Development are generally used. For these scales, the mean and standard deviation are 100 ± 15 ; 85–115 is average, 79–84 is low average; 68–78 is borderline, and 67 or less is the range of mental retardation. It is well known that average values move higher over time for all of these scales, requiring periodic readjustment of norms. This also emphasizes the need for appropriate control groups for research studies. The Vineland Adaptive Behavior Scales, based on parent report, provide normative data for infants through age 18 years on developmental levels in four domains: communication, daily living skills, socialization, and motor skills.

Children with IQs between 1 and 2 SDs below the mean learn information at a slower rate than same-age peers, and typically need support services within the general education classroom. Significant skill discrepancies may exist, and this group of children is often considered “overlooked” in public schools. When IQs are 2 SDs or more below the mean, criteria are met for mental retardation. Of this group, 85% are classified as mildly retarded.

Among the studies just discussed, a downward shift of IQ averaging 7 to 10 points has been documented, thereby increasing the number of measurements below 85. According to the National Association of School Psychologists, children with borderline IQs are at greater risk for high school dropout, aggression/conduct problems, drug use, and teenage pregnancy. If this downward IQ shift among children of thyroid-deficient mothers can be prevented, therefore, an important benefit would be achieved.

Tables 2 and 3 display reasonable test batteries, the first for infants and the second for children. They may be viewed as a first step toward achieving agreement on common panels to be used by all investigators for ease of comparison. Reliable IQ test results for research purposes can be anticipated beginning at age 7 years. The influence of home environmental factors, such as maternal depression, become less as the child becomes older and spends more time outside of the home. A graduate student may administer the tests, but a psychologist is needed to do the interpretation.

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