Assessing infant cognitive development after prenatal iodine supplementation[1–3]

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ABSTRACT

Little information is available on infant behavioral development outcomes of prenatal iodine supplementation in regions of mild to moderate iodine deficiency. Studies performed to date, all of which relied on global developmental assessments, have yielded inconsistent findings with regard to psychomotor development, negative findings with regard to mental development, and no information as to the development of specific cognitive functions. Our review of these studies leads us to suspect that the use of global developmental assessments might partially explain the negative and inconsistent findings. To identify cognitive processes that might be sensitive to prenatal iodine supplementation, we examined the timing of thyroid hormone action on specific brain systems. The development of infant visual attention is sensitive to thyroid hormone during the early prenatal period, when the fetus is entirely dependent on maternal thyroid hormone. For this reason, infant visual attention has the potential to be a sensitive measure of infant outcomes in prenatal iodine supplementation studies. We suggest the assessment of infant visual attention, with follow-up examination of childhood executive functions, as a means of capturing the effects of maternal iodine deficiency and prenatal iodine supplementation on specific cognitive processes. In particular, we propose comparison of infant performance on global developmental tests and specialized tests of visual attention in pilot trials of prenatal iodine supplementation in regions of mild to moderate iodine deficiency. Only by comparing the 2 types of tests side by side will it be possible to establish whether the use of a sensitive measure of infant visual attention will increase the reliability of such supplementation studies. Recognizing that exposure misclassification may also provide a partial explanation for the inconsistent neurodevelopmental outcomes in previous studies, we suggest that urinary iodine concentration or creatinine-corrected iodine excretion be monitored regularly in such trials throughout the prenatal period. *Am J Clin Nutr* 2016;104(Suppl):928S–34S.

Keywords: Bayley scales, brain systems, cognitive behaviors, infant neurodevelopment, prenatal nutrition

INTRODUCTION

There is insufficient information on the effects of prenatal iodine supplementation on the neurobehavioral development of young children in regions of mild to moderate iodine deficiency (1–3). As discussed by other authors in this supplement issue, there is an acknowledged need for additional studies in such regions, especially from well-designed clinical trials (4).

In **Table 1**, we list 6 standardized global tests of behavioral development (also called global developmental assessments) frequently used in psychological research studies conducted in infants. These are standardized scales of attainment with composite subscales encompassing multiple functions. We performed a PubMed search for journal articles that reported on studies of prenatal iodine supplementation that used any of these global tests; this search identified 6 studies that used the Bayley Scales of Infant Development (BSID)[6] (5–10), 1 study that used the Brunet-Lézine scale (11), and none that used any of the other tests surveyed (Table 1). The most recent comprehensive review of studies that assessed the effect of prenatal supplementation in regions of mild to moderate iodine deficiency on infant behavioral development outcomes (1) did not report on any that are not identified in Table 1. Thus, it may be that all such studies to date have used the BSID or the Brunet-Lézine scale.

The BSID edition used by the studies identified in Table 1 (BSID-II) assesses both psychomotor and mental development, whereas the Brunet-Lézine scale assesses only psychomotor development. Neither the BSID-II nor the Brunet-Lézine scale assesses the development of specific cognitive functions. In this article, we consider neurodevelopmental events that depend on maternal thyroid hormone (and thus maternal iodine status) in the early prenatal period, the development of cognitive functions associated with those events, and whether specialized cognitive tasks might be more useful than the BSID for assessing the potential effects of prenatal iodine supplementation on those cognitive functions.

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[6] Abbreviations used: BSID, Bayley Scales of Infant Development; MDI, Mental Development Index; PDI, Psychomotor Development Index; UIC, urinary iodine concentration.

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TABLE 1
Six standardized, global tests of behavioral development and prenatal iodine supplementation studies that reported their use[1]

	Target age ranges	Inventories and subscales	Prenatal iodine supplementation studies reporting use of test
Bayley Scales of Infant Development	1–42 mo	Cognitive, Language, and Motor, with Social-Emotional and Adaptive Behavior subtests	Velasco et al. (5), Murcia et al. (6), Rebigliato et al. (7), Santiago et al. (8), Melse-Boonstra et al. (9), and Brucker-Davis et al. (10)
Brunet-Lézine scale	2–30 mo	Posture, Coordination, Language, and Socialization	Berbel et al. (11)
Battelle Developmental Inventory	Birth to 7 y	Adaptive, Personal-Social, Communication, Motor, and Cognitive	None identified
Denver Developmental Screening Test	2 wk to 6 y	Fine Motor-Adaptive, Gross Motor, Personal-Social, and Language	None identified
Sequenced Inventory of Communication Development	4–48 mo	Receptive Communication Age and Expressive Communication Age	None identified
MacArthur-Bates Communicative Development Inventories	8–18 mo (Infant form); 16–30 mo (Toddler form)	Vocabulary, Word Use, Grammar, Irregular Words, Overregularized Words, Word Combination, Sentence Length, and Sentence Complexity	None identified

[1]Prenatal supplementation studies were identified by searching PubMed for "iodine" and the name of the global behavioral development test.

Writing primarily with regard to prenatal supplementation with DHA, an omega-3 PUFA, Colombo and colleagues (12–15) proposed that specialized tasks or measures designed to assess specific cognitive functions may be more sensitive than global developmental assessments for identifying the potential effects of nutrient interventions on those cognitive functions. Gould et al. (16) recently conducted a randomized controlled clinical trial in which the effects of prenatal DHA supplementation on sensitive measures of attention and of working memory and inhibitory control were assessed in the offspring at 2–3 y of age. Contrary to their working hypothesis, Gould et al. found no effect of prenatal DHA supplementation on the children's performance on these specialized cognitive tasks. However, the discrepancies between their findings and those of 2 earlier studies that assessed performance on similar cognitive tasks (17, 18) suggest that exposure misclassification may have been an issue. In the earlier studies, both of which were attached to a single randomized clinical trial, the supplementation group consumed eggs high in DHA, whereas the control group consumed ordinary eggs. Following delivery, the DHA concentration in each woman's erythrocyte membranes (a biomarker of exposure) was measured and the women were dichotomously categorized around the median value. When tested at age 12–18 mo, the children whose mothers had high-DHA erythrocytes at birth performed better on the endogenous measures of attention evaluated than did those whose mothers had low-DHA erythrocytes (17, 18). Surprisingly, there was no association between high-DHA erythrocytes at delivery and the consumption of high-DHA eggs during pregnancy; biological exposure to DHA was independent of the consumption of high-DHA eggs (17). In the study by Gould et al. (16), no biomarker of DHA exposure was used; thus, it is possible that biological exposure to DHA in the 2 groups was not well explained by the study's exposure categories, leading to exposure misclassification.

Zhou et al. (2) recently expressed the view that it might not be possible to conduct meaningful clinical trials of prenatal iodine supplementation in developed countries (i.e., where mild to moderate iodine deficiency has been found) because the use of prenatal iodine supplements in such countries has become widespread. This situation makes it difficult or impossible to classify iodine intake accurately without monitoring iodine status throughout the study. Although, as discussed elsewhere in this supplement issue, multiple-day measurement of urinary iodine concentration (UIC) or 24-h urinary iodine excretion can be useful for assessing individual iodine status, the UIC measured in a single spot urine sample is not considered to be a reliable biomarker of individual iodine status because UIC reflects only recent iodine intake, which can vary widely from day to day (19). Nevertheless, the measurement of UIC or creatinine-corrected urinary iodine excretion at each clinic visit in prenatal supplementation trials could be used to identify participants who take daily iodine supplements, irrespective of whether those supplements are study-related, and thus could be used to reduce exposure misclassification.

Although we address only behavioral outcomes in this article, there is added value in the simultaneous use of noninvasive physical methods to examine neurophysiologic indicators of such outcomes. We refer the reader to our own group's work on the use of the electroencephalogram in research on cognitive development (20).

Studies of prenatal brain development have implications for the specific cognitive functions that, we propose, are better indicators of infant cognition outcomes than global developmental tests. In another article in this supplement issue, Bauer and Dugan (21) discuss the effects of maternal iodine deficiency on hippocampal development in the rat and suggest that aspects of memory associated with the hippocampus may be affected. Like us, they propose that sensitive measures of specific cognitive functions (rather than global developmental tests) be used for evaluating the cognitive effects of prenatal iodine supplementation.

In the present article, we first examine prenatal brain development and the timing of thyroid hormone action on specific brain systems in relation to iodine deficiency. Next, we look at infant neurobehavioral development outcomes in prenatal supplementation studies conducted in regions of mild to moderate iodine deficiency, with a focus on methodologic limitations, including the

use of global developmental assessments. Within the same section, we also discuss a study that analyzed the association between child cognitive outcomes and maternal iodine status during pregnancy. We then discuss the rationale for investigating specific cognitive processes during infancy, followed by consideration of infant attention in relation to child executive function and related childhood outcomes. Finally, we provide our conclusions and recommendations.

PRENATAL BRAIN DEVELOPMENT AND THE TIMING OF THYROID HORMONE ACTION

Iodine is an intrinsic component of thyroid hormone. Maternal iodine deficiency can lead to inadequate maternal thyroid hormone production. The impact on prenatal brain development depends on the timing and severity of the iodine deficiency (3, 22).

In humans, brain development begins ~2 wk after conception with the transformation of undifferentiated tissue in the outer layer of the embryo into nervous system tissue. As part of this process, the neural tube is formed around gestational day 18, differentiating brain and spinal cord tissue. The development of the brain's cortex begins with the formation of the most anterior part of the neural tube, the prosencephalon, at ~4 wk after conception (23). By the end of week 4, maternal thyroid hormone can be found in embryonic cavities (24). The fetal thyroid starts developing at approximately week 12 and the fetal thyroid is capable of producing thyroid hormone by approximately week 20 (25). This timeline is critical because it means that during the early stages of brain development, the fetus must depend solely on maternal thyroid hormone for neurological development. During early prenatal development, maternal thyroid hormone promotes neuronal proliferation and neural migration in the cerebral cortex and hippocampus (26). After the fetal thyroid becomes functional, both maternal thyroid hormone and fetal thyroid hormone promote further neurogenesis and neural migration, axonal growth, dendritic branching and synaptogenesis, glial cell differentiation and migration, and the production of oligodendrocyte precursor cells that form the myelin sheath (22, 26).

The influence of maternal thyroid hormone and neonatal thyroid hormone on neurological development is critical to the specific neural systems formed during early brain development. It appears that the neural substrates of cognitive abilities that depend on the visual system are vulnerable to deficits in thyroid hormone during the first and second trimesters (27). Basic infant visual processes such as contrast sensitivity seem to be dependent on the adequacy of maternal thyroid hormone concentrations in early gestation, when no fetal thyroid hormone is present, whereas infant visuospatial processing abilities are dependent on the adequacy of neonatal thyroid hormone concentrations. This means that infant visual attention abilities are sensitive to thyroid hormone during the prenatal period of greatest dependence on the maternal source (27).

Preferential uptake of circulating iodide by the placenta may diminish the effects of moderate maternal iodine deficiency on the fetus after the fetal thyroid becomes functional (28). However, whether or not the fetus becomes less sensitive to maternal iodine deficiency after beginning to produce thyroid hormone, the developmental events that take place before the maturation of the fetal thyroid are potentially useful targets for assessing the effects of iodine supplementation. Thus, because of its developmental window, infant visual attention is a discrete aspect of infant information processing that has the potential to be a sensitive measure of infant outcomes in prenatal iodine supplementation studies.

BEHAVIORAL DEVELOPMENT OUTCOMES OF PRENATAL IODINE SUPPLEMENTATION OR MATERNAL IODINE STATUS IN REGIONS OF MILD TO MODERATE IODINE DEFICIENCY

In the first part of this section, we examine the studies conducted in regions of mild to moderate iodine deficiency that assessed the association between infant behavioral development and prenatal iodine supplementation. All of these studies used a global developmental assessment, either the BSID or the Brunet-Lézine scale (see Table 1). We then examine a single study that assessed the association between child cognitive development and maternal iodine status during pregnancy.

Infant behavioral development

The infant behavioral development outcomes reported in 6 of the 7 articles identified in Table 1 are summarized in **Table 2**; the remaining article describes a study in progress for which results have not yet been published (9). We are unaware of any other studies of prenatal iodine supplementation conducted in regions of mild to moderate iodine deficiency in which behavioral development endpoints were assessed in infants.

Two observational studies are summarized in Table 2. The earlier of these, conducted in Valencia, Spain, unexpectedly found lower scores on the Psychomotor Development Index (PDI) of the BSID in association with higher prenatal supplementary iodine; stratification by sex showed that the association was confined to girls (6). The subsequent study, conducted in 3 other Spanish cities by the same research group, found lower scores on the PDI in association with higher prenatal supplementary iodine in 1 city but not in the other 2 cities; unlike the earlier study, no dependence on sex was found (7). Both of the studies found no association of infant scores on the Mental Development Index (MDI) of the BSID with prenatal iodine supplementation (6, 7). Neither study included a nonsupplemented control group, which adds to the difficulty of interpretation. The confusing findings from these 2 observational studies underscore the need for randomized controlled clinical trials. In these and other observational studies, it can be difficult or impossible to isolate the effects of iodine supplementation from those of other prenatal and postnatal factors known to affect infant behavioral development.

Four interventional studies are summarized in Table 2. Of these, 2 found a positive association between infant behavioral development and prenatal iodine supplementation (5, 11) and 1 study found no association (10). In the remaining interventional study, iodine supplementation plus iodized salt use yielded no improvement in infant behavioral development scores compared with iodized salt use alone (8). But because all of the groups were advised to use iodized salt in cooking and at the table, this study is uninformative as to the effect of iodine supplementation in the absence of such intervention. In the interventional study that found no association between infant behavioral development and prenatal iodine supplementation, children were tested at age 2 y

TABLE 2
Infant behavioral development outcomes of prenatal iodine supplementation studies in regions of mild to moderate iodine deficiency[1]

Study design and location (ref)	Iodine supplementation	Infant ages at testing[2]	Behavioral development outcomes[3]	Comments
Interventional study in Andalusia, Spain (5)	From first trimester through lactation: 300 μg/d (S), 0 μg/d (control)	5 ± 3 mo (S), 12 ± 5 mo (control)	S had higher PDI ($P = 0.02$) and behavior more in agreement with age group for producing sounds by banging ($P = 0.001$), cooperation ($P = 0.008$), activity ($P = 0.01$), reaction to persons ($P = 0.02$), arousal ($P = 0.04$), and reaction to the mother ($P = 0.05$). No significant difference in MDI.	Large intergroup difference in infant age at testing; PDI scores in S infants correlated with breastfeeding
Observational study in Valencia, Spain (6)	Estimated: <100 μg/d (S1), 100–149 μg/d (S2), ≥150 μg/d (S3)	11–16 mo	S3 had lower PDI than S1 ($P = 0.002$), associated only with girls ($P < 0.001$). S3 had a higher rate of PDI <85 than S1 ($P = 0.013$). No significant difference in MDI.	No nonsupplemented control group
Observational study in Asturias, Gipuzkoa, and Sabadell, Spain (7)	Estimated: 0–100 μg/d (S1), 100–149 μg/d (S2), ≥150 μg/d (S3)	12–30 mo (16 mo)	S3 in Asturias (but not the other 3 cities) had lower PDI than S1 ($P < 0.05$). No significant difference in MDI.	No nonsupplemented control group
Randomized clinical trial in Jaen, Spain (8)	From GW <10: IS use (S1), 200 μg/d (S2), 300 μg/d (S3)[4]	13 ± 5 mo	No significant difference in PDI or MDI.	No control group not receiving IS
Pilot study in children recruited from a randomized clinical trial in Nice, France (10)	From GW <10 through 3 mo postpartum: 150 μg/d (S), 0 μg/d (control)	23–25 mo (24 mo)	No significant difference in any scale or subtest of the BSID.	Small study population ($n = 44$)
Interventional study in Alicante, Spain (11)	S1: from GW 4–6; S2: from GW 12–14; S3: from delivery; 153 μg/d (all)	18 mo	S1 had higher DQ overall than S3 ($P < 0.001$) and S2 ($P < 0.05$). S1 had higher DQ than S3 for the gross and fine motor coordination subscales and the socialization subscale ($P < 0.001$ for each) but not the language subscale.	Study population was small ($n = 44$) because of strict inclusion criteria; study was well designed

[1]BSID, Bayley Scales of Infant Development; DQ, developmental quotient; GW, gestational week; IS, iodized salt; MDI, Mental Development Index; PDI, Psychomotor Development Index; ref, reference; S, supplemented group.

[2]Values are means ± SDs, ranges, or means.

[3]Criterion for significance was $P < 0.05$. The P values shown were reported by the cited studies. DQs are age-adjusted scales of the Brunet-Lézine Scale. The MDI and PDI are age-adjusted scales of the BSID.

[4]All groups received the recommendation to use IS in cooking and at the table.

(10), whereas in the 2 interventional studies that found an association, children were tested at age 18 mo (11) or younger (5).

One of the 2 positive interventional studies used the BSID. In that study, the infants of mothers supplemented with iodine had higher PDI scores ($P = 0.02$) than did those whose mothers were not supplemented; the supplemented group had behavior more in agreement with age group for producing sounds by banging ($P = 0.001$), cooperation ($P = 0.008$), activity ($P = 0.01$), reaction to persons ($P = 0.02$), arousal ($P = 0.04$), and reaction to the mother ($P = 0.05$). There was no difference in MDI scores (5). The results of this study were confounded by the age differential at testing; on average, the supplemented group was >2 times as old as the control group at behavioral assessment (mean ages of 13 and 5 mo, respectively). In addition, the PDI scores of the supplemented group were found to correlate with breastfeeding, suggesting that the results may have been confounded by postnatal exposure to iodine as well as factors associated with breastfeeding.

The other positive interventional study used the Brunet-Lézine scale, which, as noted in the Introduction, assesses psychomotor development but, unlike the BSID, does not include a mental development index. The study found higher developmental quotients in the offspring of women supplemented with iodine starting at 4–6 wk of gestation than in those starting at 12–14 wk of gestation or after delivery. Compared with the latter group, infants in the early-supplementation group had higher developmental quotients for the gross and fine motor coordination subscales and the socialization subscale ($P < 0.001$) but not the language subscale (11). This was a well-designed study, although the study population was small ($n = 44$) because of strict inclusion criteria. The study is informative with respect to the measures assessed by the Brunet-Lézine scale but uninformative with respect to potential effects on mental or cognitive development.

All of the studies summarized above and in Table 2 had methodologic issues that impede their interpretation, including the use of the BSID or the Brunet-Lézine scale. The studies that found an increase in psychomotor development with supplementation failed to find an increase in mental development, which could mean that there was actually no effect

on mental development or that the cognitive processes affected are poorly measured by the MDI. With regard to the well-designed study (11) that might be the most informative with respect to the behavioral outcomes evaluated, the global assessment used contained no index of mental or cognitive development.

Child cognitive development

As discussed above, we are unaware of any studies in which specific cognitive assessments, as opposed to global measures of behavioral developmental, were used to evaluate the potential cognitive effects of prenatal iodine supplementation in regions of mild to moderate iodine deficiency. However, several studies found associations between mild to moderate maternal iodine deficiency during pregnancy and cognitive development in school-aged children as measured by global developmental tests (3). One observational study examined 2 child cognitive outcomes, intelligence quotient at age 8 y and reading ability at age 9 y, in relation to maternal urinary iodine excretion in the first trimester of pregnancy (29). The women were dichotomized around a urinary iodine-to-creatinine ratio of 150 μg/g. After adjustment for 21 potentially confounding variables (including breastfeeding), the children from the low-iodine group were found to be more likely to have scores in the lowest quartile for verbal intelligence quotient ($P = 0.02$), reading accuracy ($P = 0.007$), and reading comprehension ($P = 0.02$) than those from the high-iodine group. Further stratification of the low-iodine mothers around an iodine-to-creatinine ratio of 50 μg/g showed that children from the group with ratios <50 μg/g had lower scores than those from the group with ratios of 50–150 μg/g, indicating that the study results were internally consistent.

RATIONALE FOR STUDYING SPECIFIC COGNITIVE PROCESSES DURING INFANCY

As discussed above, studies that used the BSID have yielded inconsistent findings in the prenatal iodine supplementation literature. Whether or not the BSID is partially responsible for this inconsistency remains to be determined. We suggest that more reliable results may be obtained in future studies if the testing process can be linked to explicit neural systems most likely to be affected by any thyroid hormone inadequacy that might accompany mild to moderate maternal iodine deficiency during pregnancy. Thus, there is a need to assess cognitive performance during infancy in the information-processing domains that are the most likely to be affected (30).

This is not a novel proposal. As discussed in the Introduction, Colombo and colleagues (12–15) proposed that global developmental assessments are of less value for assessing nutrient interventions than outcome measures narrowly targeted to specific brain systems. On the other hand, global developmental assessments such as the BSID are invaluable in determining a child's current level of functioning. They are especially helpful in diagnosing infants with developmental delays and thus are critical as screening devices for early intervention. The predictive value of the BSID is greater for high-risk infants than for typically developing infants and greater if administered after 12 mo of age than during early infancy (31). Thus, the BSID reflects developmental status but probably not specific cognitive skills that might be improved by prenatal nutritional interventions.

In part because of their convenience, global developmental assessments, and especially the BSID, are widely used. The BSID and other common global assessments are standardized and, with the purchase of a test kit, a trained clinician can conduct the assessment in a consistent manner in any locale. By contrast, tasks designed to assess infant cognition are typically nonstandardized laboratory measures developed by individual researchers; in the absence of formal training, measurement of performance on such tasks might differ substantially across research laboratories, leading to inconsistent results (12). Furthermore, there are no developmental score charts or pass/fail indicators because, in general, the tasks are designed to capture wide-ranging individual differences in some aspect of infant cognitive function rather than measure performance against a given standard.

Despite the relative inconvenience of current tests of specific infant neurobehavioral processes, there is a need for such tests to be conducted in parallel with the BSID in future iodine supplementation studies. Only then will it become clear whether inconsistent findings in the prenatal iodine supplementation literature are in part attributable to the use of the BSID.

Whereas the BSID is suitable for infants between 1 and 42 mo of age, tasks designed to tap specific infant cognitive processes are much narrower in their age appropriateness. For example, infant information-processing tasks that target attention and memory are developmentally appropriate for the first 8 or 9 mo but are probably not useful for older infants (14). Attempts at translating such tasks to older ages do not always yield age-appropriate measures (16).

On the basis of our survey of the literature reported here, it seems likely that infant visual attention is among the infant cognitive processes that are most sensitive to maternal iodine deficiency and prenatal supplementation. Although cognitive processes are measured differently in infants and children, there is substantial evidence that certain measures of infant visual information processing, such as attention, habituation, and recognition memory, are related to childhood cognitive processing of language, memory, and intelligence. Thus, specific abilities in infancy may be early evidence of their more mature counterparts, both behaviorally and neurologically (32).

INFANT VISUAL ATTENTION IN RELATION TO CHILD EXECUTIVE FUNCTION

Currently, it is unclear which particular aspect of infant visual attention is likely to yield the most information with respect to nutrition intervention studies. Attention is multidimensional; purposeful, voluntary attention likely entails the integration of low-order attentional systems with memory functions, mediated by frontal lobe processes (15). For example, in the developmental science literature, there are 2 attention networks that are conceptually and neurologically germane to research with infants and children. The orienting attention network is responsible for the selection of sensory inputs and becomes functionally mature between 3 and 6 mo of age. This attention network allows the infant to disengage fixation, shift attention to another location, and reengage focus. The executive attention network is responsible for the resolution of conflicts among response

TABLE 3
Examples of the use of laboratory measures of infant visual attention, by the attention network addressed

	Location (general brain areas)	Appropriate infant age at testing	Information-processing skills tested	Laboratory measures (cognitive tasks)
Orienting network	Parietal lobes	3–9 mo	Disengage, shift, refocus	Habituation tasks, looking time tasks, shift rate tasks (32–34)
Executive network	Frontal lobes	From 8 mo	Resolution of conflict	A-not-B tasks, problem-solving tasks[1] (35, 36)

[1]Although not previously linked with the executive attention network, problem-solving tasks tap higher-order processes and require voluntary control of attention (12).

tendencies; it emerges during the latter half of the first year and continues to develop into early childhood. In infancy, there is overlap in the functional connectivity of these 2 attention networks, which become more synchronized by early childhood. Examples of the use of laboratory measures of infant visual attention that address each of these attention networks are provided in **Table 3**. Note that infant visual attention is not a unitary function; different aspects are tapped by different tasks. Ideally, all facets of infant visual attention should be tested for their potential sensitivity to prenatal iodine supplementation in regions of mild to moderate iodine deficiency.

Two examples of the measurement of infant visual attention and its use for predicting executive functions (higher-order cognitive processes associated with frontal lobe functioning) show the value of infant visual attention assessment in the prediction of later cognitive outcomes. In one study, typically developing 5-mo-old infants were presented with a visual stimulus, and looking time was measured. Infants who were quicker at processing the stimulus during this visual attention task had better performance on executive function tasks at ages 2, 3, and 4 y, even after the investigators controlled for the contributions of verbal intelligence to executive function performance (33). A second study pushed the predictivity of infant visual attention to preadolescence. Infants' speed at processing a visual stimulus was assessed at both 7 and 12 mo and included the rapidity with which information was encoded. Greater processing speed at both ages during infancy was associated with better performance on executive function tasks at age 11 y (32). Together, these studies implicate early visual attention processes in the development of later executive functions. Executive functions are strongly related to school performance in reading and mathematics, suggesting that infant visual attention skills are part of the foundation for successful academic achievement.

CONCLUSIONS AND RECOMMENDATIONS

The prenatal iodine supplementation studies conducted in regions of mild to moderate iodine deficiency have reported inconsistent findings with regard to psychomotor development, negative findings with regard to mental development, and no information as to the development of specific cognitive functions. All of the studies used global developmental assessments; in 6 of 7 studies this was the BSID. In regions of mild to moderate iodine deficiency, any improvement in cognitive function produced by prenatal iodine supplementation might be small and narrowly confined to skills that are an expression of a specific neurological process. On the basis of the literature reporting its use, the BSID is not a sensitive tool for measuring developmental differences in specific cognitive tasks or skills (31).

To identify specific cognitive functions that might be more sensitive to prenatal iodine supplementation, we examined the timing of thyroid hormone action on specific brain systems. Infant visual attention abilities are sensitive to thyroid hormone during the early prenatal period, when the fetus is entirely dependent on maternal thyroid hormone. For this reason, infant visual attention has the potential to be a sensitive measure of infant outcomes in prenatal iodine supplementation studies.

We anticipate that the use of sensitive measures of infant visual attention in prenatal iodine supplementation studies will improve the reliability of infant developmental outcomes in such studies, particularly in regions of mild to moderate iodine deficiency, where less sensitive tests have yielded inconsistent results. If infant visual attention is shown to be affected by prenatal iodine supplementation, then its use for predicting higher-level cognitive outcomes later in childhood should be explored.

Unlike the BSID and other global developmental assessments typically used in supplementation research, the cognitive tasks we propose are not standardized. This means that an individual infant's score cannot be compared with a chart of percentiles previously established for ranking or establishing a developmental age. Clinicians and other researchers interested in studying the developmental effects of prenatal iodine supplementation would be wise to enter into multidisciplinary collaborations with developmental cognitive neuroscientists who are experienced at assessing infant performance on the types of cognitive tasks proposed here. We anticipate that such interdisciplinary efforts would greatly benefit research on prenatal iodine supplementation.

We propose that infant performance on global developmental tests and specialized tests of visual attention be compared in pilot trials of prenatal iodine supplementation in regions of mild to moderate iodine deficiency. Only by comparing the 2 types of tests side by side will it be possible to establish whether the use of a sensitive measure of visual attention will increase the reliability of supplementation studies. Recognizing that exposure misclassification may be partially to blame for inconsistent neurodevelopmental outcomes in previous studies (2), we suggest that UIC or creatinine-corrected urinary iodine excretion be monitored regularly throughout the prenatal period so as to identify control participants who take supplements outside of the trial as well as supplemented participants who fail to take trial-assigned supplements.

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