Research needs for assessing iodine intake, iodine status, and the effects of maternal iodine supplementation[1,2]

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ABSTRACT

The Office of Dietary Supplements of the NIH convened 3 workshops on iodine nutrition in Rockville, Maryland, in 2014. The purpose of the current article is to summarize and briefly discuss a list of research and resource needs developed with the input of workshop participants. This list is composed of the basic, clinical, translational, and population studies required for characterizing the benefits and risks of iodine supplementation, along with related data, analyses, evaluations, methods development, and supporting activities. Ancillary studies designed to use the participant, biological sample, and data resources of ongoing and completed studies (including those not originally concerned with iodine) may provide an efficient, cost-effective means to address some of these research and resource needs. In the United States, the foremost question is whether neurobehavioral development in the offspring of mildly to moderately iodine-deficient women is improved by maternal iodine supplementation during pregnancy. It is important to identify the benefits and risks of iodine supplementation in all population subgroups so that supplementation can be targeted, if necessary, to avoid increasing the risk of thyroid dysfunction and related adverse health effects in those with high iodine intakes. Ultimately, there will be a need for well-designed trials and other studies to assess the impact of maternal supplementation on neurodevelopmental outcomes in the offspring. However, 2 basic information gaps loom ahead of such a study: the development of robust, valid, and convenient biomarkers of individual iodine status and the identification of infant and toddler neurobehavioral development endpoints that are sensitive to mild maternal iodine deficiency during pregnancy and its reversal by supplementation. *Am J Clin Nutr* 2016;104(Suppl):941S–9S.

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INTRODUCTION

The NIH Office of Dietary Supplements held 3 workshops on iodine nutrition in Rockville, Maryland, in April, July, and September 2014 (1). The primary purpose of the workshops was to consider the research and resources necessary to evaluate the clinical and public health benefits and risks of maternal iodine supplementation in the United States. The first workshop focused on the assessment of iodine intake, the second focused on the assessment of iodine status, and the third focused on clinical trials of maternal iodine supplementation with infant neurodevelopmental outcomes. An introductory article (2) provides the background of the Office of Dietary Supplements' Iodine Initiative, summarizes the 3 workshops, and introduces the resulting 12 articles, which are also published in this supplement issue.

The purpose of the current article is to summarize and briefly discuss a list of research and resource needs that were brought to light by the workshops and, in some cases, by the resulting articles. Methodologic issues and data gaps were introduced and discussed in the course of presentations, question-and-answer sessions, and moderated sessions. A draft list of the research and resource needs developed at each workshop, amended with information from the resulting manuscripts and other sources, was circulated to participants. The final list of research needs was improved by using suggestions received from workshop participants.

RESEARCH AND RESOURCE NEEDS

Text Boxes 1, **2**, and **3** provide a hierarchy of research and resource needs corresponding, with some overlap, to the topics discussed at the first, second, and third workshops, respectively. This hierarchy can also be viewed as a pragmatic sequence (or approximation thereof) for conducting research and developing resources. The research and resource needs listed in the text boxes are described more fully in the following sections.

Iodine content of US foods and drinking water supplies

Addition of iodine measurement to large, ongoing food surveys

Data on the nutrient composition of the >8700 distinct foods and food components analyzed by the USDA's National Food and Nutrient Analysis Program (NFNAP)[5] are reported in the National Nutrient Database for Standard Reference, which, among

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[2] The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the NIH or the US Department of Health and Human Services.

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[5] Abbreviations used: CRM, Certified Reference Material; DBS, dried blood spot; FDA, US Food and Drug Administration; FT4, free thyroxine; NFNAP, National Food and Nutrient Analysis Program; NIST, National Institute for Standards and Technology; SRM, Standard Reference Material; TDS, Total Diet Study; TSH, thyroid-stimulating hormone; UIC, urinary iodine concentration; UIE, urinary iodine excretion.

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Text Box 1 Research and resources needed for assessing the iodine concentrations of US foods and drinking water supplies, iodine intakes, and iodine requirements

Iodine concentrations in US foods and drinking water supplies

- Addition of iodine measurement to large, ongoing food surveys
- Evaluation of the contribution of agricultural practices to the adventitious iodine content of high-iodine foods
- Identification of means for reducing iodine loss from iodized table salt
- Evaluation of salt iodation as an alternative to iodization
- Assessment of the variability in food iodine concentrations associated with iodine-containing food additives
- Development of proposed guidelines for the iodine content labeling of foods
- Periodic measurement of iodine in US drinking water supplies

Iodine intake in US population subgroups

- Incorporation of food iodine variation into estimates of iodine intake
- Evaluation of iodine intake from table salt
- Assessment of iodine intake from prenatal dietary supplements
- Development, testing, and verification of iodine intake questionnaires

Assessment of the relation between supplemental iodine and breast-milk iodine

Assessment of the role of dietary patterns in iodine deficiency

Iodide uptake inhibitor effects and thresholds

- Assessment of the relation between maternal exposures to iodide uptake inhibitors and the iodine content of breast milk
- Assessment of the relation between maternal exposures to iodide uptake inhibitors and maternal iodine status during pregnancy

its many uses, provides the nutrient data for NHANES (3). Currently, iodine is not among the nutrients analyzed by the NFNAP, but steps toward its inclusion are in motion. The USDA's Nutrient Data Laboratory recently qualified a commercial laboratory to measure the iodine concentrations of foods by using inductively coupled–plasma mass spectrometry, an accurate and cost-effective method (4).

The US Food and Drug Administration's (FDA's) Total Diet Study (TDS) measures the concentrations of iodine and other nutrients in 286 foods collected quarterly from 4 regions of the United States. Lately, the FDA has begun working with the Nutrient Data Laboratory to harmonize procedures such that the food-composition data gathered by the TDS can be included in the National Nutrient Database for Standard Reference (4).

Text Box 2 Research and resources needed for assessing individual iodine status and conducting iodine supplementation studies

Development of biomarkers of individual iodine status

Conduct of clinical studies with multiple approaches to assessing individual iodine status

Conduct of clinical studies to inform safe upper limits on chronic iodine intake

Materials, tools, and other resources for assessing iodine status and thyroid function

- Development of subgroup-specific biological sample pools
- Development of reference materials for biological samples
- Standardization and harmonization of thyroid function tests
- Development of statistical approaches for improving estimates of iodine deficiency and excess

Materials, tools, and other resources for conducting iodine supplementation studies

- Development of reference materials for dietary supplements
- Development of point-of-care tests for assessing urinary iodine concentration (UIC) and thyroid function
- Development of frozen meals with specified iodine content

Text Box 3 Clinical studies and supporting research to assess the effects of prenatal iodine supplementation on neurobehavioral development

Evaluation of neurobehavioral development outcomes of maternal hypothyroxinemia in previous studies

Tools for assessing the effects of prenatal iodine supplementation on neurobehavioral development in infants and toddlers

- Evaluation and validation of established tasks for assessing the development of specific neurobehavioral functions in infants and toddlers
- Development and validation of assessment tools for children <3 y old for addition to the NIH Toolbox for the Assessment of Neurological and Behavioral Function

Evaluation, selection, and use of neurobehavioral development tests as outcome measures in clinical trials of prenatal iodine supplementation

- Conduct of clinical studies to evaluate the sensitivity of infant and toddler neurobehavioral development assessment tools to maternal iodine deficiency
- Conduct of prenatal iodine supplementation trials to assess neurobehavioral development outcomes in infants and toddlers

It would be useful to understand the extent to which the iodine content of iodine-fortified foods, processed foods, and foods containing adventitious iodine has changed over the previous few decades. To gather data on changes over time, possibly the iodine concentrations of important dietary sources could be investigated by analyzing stored food samples collected by the NFNAP, the TDS, or similar data-collection efforts.

Agricultural practices affecting adventitious iodine in high-iodine foods

Most of the iodine in cow milk (5, 6) and chicken eggs (7) in the nation's food supply appears to be contributed by feed supplements. The 1% iodine solution used to spray bovine teats for disinfection purposes may also materially add to the iodine content of cow milk (6). Currently, adventitious iodine in foods is not addressed by any public health policy, even though dairy products and eggs are important sources of dietary iodine in the US population (4). The amount of adventitious iodine present in dairy products and eggs might be decreasing in response to changing agricultural practices. It would be useful to document any such decreases and their likely effect on iodine intake and iodine deficiency.

Identification of means for reducing iodine loss from iodized table salt

The FDA allows the use of iodide salts (cuprous iodide and potassium iodide) in the fortification of table salt, a process known as iodization (8). Unfortunately, the iodine concentration of iodized table salt is unstable and highly variable; under ordinary storage conditions, the loss of iodine is strongly dependent on humidity (9). Research is needed on packaging and storage practices to reduce iodine loss. The efficacy of packaging smaller quantities for retail sale and labeling with an iodine expiration date also might be explored.

Evaluation of salt iodation as an alternative to iodization

Although iodate compounds are more stable than iodide compounds and are used in other countries for the fortification of table salt (10), at the present time the FDA has not approved such use in the United States. Clarification is needed as to the pros and cons of salt iodation and—if warranted from a public health standpoint—the practical barriers to its approval and adoption. Models that incorporate rates of iodine loss from iodized salt compared with iodated salt could be useful for predicting the impact of iodation on iodine deficiency and excess across population subgroups.

Variability in food iodine concentrations associated with food additives

Although it is clear that iodine-containing food additives (e.g., alginates; iodate dough conditioners; and erythrosine, an organoiodine color additive) can contribute materially to the iodine content of commercial breads and other baked goods (4), quantitative information is lacking on the variability in food iodine concentrations associated with the use of such additives (11).

Development of proposed guidelines for the iodine content labeling of foods

There is high variability in the iodine content of numerous foods that are important dietary sources in the United States, including foods (e.g., milk and eggs) in which most of the iodine is from adventitious sources (4, 11). Proposed guidelines for an iodine content labeling requirement are needed for high-iodine foods that contain a high percentage of iodine from adventitious sources or food additives. The implementation of a labeling requirement (developed with stakeholder input) should lead to increased uniformity of relevant animal husbandry and food-processing practices and, thus, less variability in iodine content.

Periodic measurement of iodine in US drinking water supplies

A wide range of iodine concentrations in public drinking water supplies has been reported (12, 13). The periodic measurement of iodine in the nation's primary drinking water supplies, in conjunction with ready public access to the resulting data, would allow improved estimation of iodine intakes from drinking water across geographic regions.

Iodine intake in US population subgroups

Incorporation of food iodine variation into estimates of iodine intake

Evaluating iodine intake by considering all dietary sources may provide a more complete understanding of the population prevalences of iodine deficiency and excess than the use of UIC data alone (14). At present, estimates of dietary iodine intake are typically based on the mean iodine concentration of each food consumed. However, reliance on a single summary statistic ignores the substantial variation in iodine concentrations of some high-iodine foods across time and geographic region. Food-composition tables should provide useful information on iodine concentration variability, including means, SDs, and medians. Ideally, food-composition databases would include all validated measurements, allowing modeling of the distribution of iodine intakes to replace summation of point estimates (11).

Evaluation of iodine intake from table salt

Because very little of the salt used by restaurants and in food processing is iodized, most iodized salt in the United States is purchased for home use at the table or in cooking (15). When iodized salt is dissolved in water and boiled, much of the iodine is lost to volatilization within 5 min (9). Thus, various common methods of food preparation (including stovetop cooking) are unlikely to preserve the initial iodine content. Information is needed on the absolute and relative amounts of dietary iodine contributed by iodized salt used in the home—both at the table and in cooking—for population subgroups at risk for iodine deficiency or excess. This requires sampling and analysis of the iodized salt used in the home by individuals; this could possibly be performed as an ancillary study attached to an ongoing dietary survey such as NHANES.

Assessment of iodine intake from prenatal dietary supplements

There is no FDA regulation at present concerning the addition of iodine to prenatal vitamins (8). It would be useful to know the US sales volumes and patterns for prescription and nonprescription prenatal dietary supplements that contain iodine as well as those that do not. Additional information is also needed on the analyzed compared with the labeled iodine content of iodine-containing prescription and nonprescription prenatal dietary supplements. In a study of nonprescription prenatal supplements purchased in 2009–2010, the analyzed iodine content was 26% higher, on average, than the labeled content (16).

Development, testing, and verification of iodine intake questionnaires

Validated questionnaires focused on iodine intake are needed for addition to automated 24-h dietary recall intake tools, dietary supplement questionnaires, and other dietary research instruments. Iodine intake questionnaires are likewise needed for screening entrants to research studies and tracking their intakes once enrolled. Similarly, iodine intake questionnaires are needed for patients undergoing diagnostic or therapeutic treatment with radioiodine.

Relation between supplemental iodine and breast-milk iodine

Some studies in moderately iodine-deficient populations, including a randomized, placebo-controlled trial conducted in New Zealand, found higher breast-milk iodine concentrations in women given a daily iodine supplement (17). Additional data are needed on the effect of supplemental iodine—iodized salt as well as dietary supplements—on breast-milk iodine in women who represent the full range of iodine intakes observed in the United States.

Role of dietary patterns in iodine deficiency

A number of foods—including eggs, dairy products, seafood, and commercial baked goods made with iodine-containing additives—are important sources of iodine in the US population (4). Diets that exclude such foods, whether for ethnic, religious, or personal reasons, may be low in iodine. Information is needed on the prevalence of mild to moderate iodine deficiency among subgroups of the US population who consume such diets.

Iodide uptake inhibitor effects and thresholds

Perchlorate, nitrate, and thiocyanate are competitive inhibitors of iodide uptake by the sodium-iodide symporter in the thyroid gland, the placenta, the lactating breast, and other tissues that concentrate iodine. Although the ability of these anions to inhibit iodide binding by the symporter has been studied in vitro (18), the relation between in vitro binding affinities to in vivo inhibition of iodide uptake is unclear (19). Perchlorate from both natural and industrial sources is found in some drinking water supplies and in a variety of foods, especially produce with a high water content, such as lettuce (20, 21). Nitrate compounds occur naturally in vegetables; these are often the principal sources of exposure to nitrate (22). In farming and agricultural regions, nitrate-contaminated drinking water can also be an important exposure source (23). Thiocyanate exposure is attributable to both dietary sources and tobacco smoke (24).

Relation between maternal exposures to iodide uptake inhibitors and the iodine content of breast milk

Thiocyanate (25) but not perchlorate (26) was found to affect the iodine concentration of breast milk in women with a median UIC in the iodine-sufficient range. The study that found no effect of perchlorate also found no effect of thiocyanate but included too few smokers for this result to be meaningful (26). Additional data are needed on the dose-related effects of thiocyanate and perchlorate on breast-milk iodine in lactating women who are mildly to moderately iodine-deficient.

Relation between maternal exposures to iodide uptake inhibitors and maternal iodine status during pregnancy

As indicated by the partially discordant findings of 2 recent investigations, the effect of iodide uptake inhibitors on thyroid function in pregnant women is unclear. The studies examined associations between urinary concentrations of the inhibitors and serum concentrations of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) in pregnant women during the first half (27) or first trimester (28) of pregnancy. The former study, conducted in New York City, reported that a weighted index of urinary

perchlorate, nitrate, and thiocyanate—but not each inhibitor concentration individually—was positively associated with TSH (27). The latter study, conducted in Thailand, found that urinary perchlorate was positively associated with TSH and negatively associated with FT4 in the overall study population, whereas urinary thiocyanate was positively associated with TSH only in the subset with UIC values <100 μg/L; nitrate was not studied (28).

It remains to be determined whether exposure to iodide uptake inhibitors increases the incidence of mild to moderate iodine deficiency in pregnant women or in any other population subgroup. The availability of a biomarker of individual iodine status (discussed below) would facilitate the study of the quantitative relation between inhibitor exposure and iodine status.

Biomarkers of individual iodine status

Because UIC measured in spot urine samples mainly reflects recent iodine intake, it is not a useful indicator of the iodine status of individuals (29). The only reliable means for assessing individual iodine status—multiple measurement of 24-h urinary iodine excretion (UIE) (30) and measurement of radioiodine uptake by the thyroid (31)—are impractical except in very small studies. One or more convenient biomarkers of individual iodine status suitable for use in clinical practice and research studies is needed, particularly for identifying mild to moderate iodine deficiency in pregnant women and in other women of reproductive age. A biomarker of individual iodine status could be used to stratify and monitor participants in clinical supplementation trials and to evaluate the health benefits and risks of fortification.

Serum thyroglobulin has shown promise as a biomarker of iodine status; further assessment of its usefulness for this purpose would require the validation of assay-specific thyroglobulin reference ranges, particularly for pregnant women (categorized by trimester) and neonates (29). Serum inorganic iodide may also be worthy of investigation (32). Together with the identification of useful biomarkers, there is a need for the development and validation of analytical methods that are accurate, precise, and reliable.

Clinical studies with multiple approaches to assessing individual iodine status

There is a need for clinical studies in which multiple approaches for assessing individual iodine status are tested in populations of pregnant women and in other women of reproductive age with a high prevalence of mild to moderate iodine deficiency. Such approaches might include the following: multiple measurement of UIC and 24-h UIE over a period long enough to represent the full range of daily values, coordinated with thyroid function testing; the use of statistical methods to account for intraindividual variation in UIC and dietary intake; combined analysis of UIC data and dietary survey data; and the use of diets with defined iodine content.

Clinical studies to inform safe upper limits on chronic iodine intake

Excessive exposures to iodine from medical sources (iodine-containing drugs and diagnostic contrast agents) and from foods or dietary supplements with an exceptionally high iodine content are associated with the development of thyroid autoantibodies and diverse thyroid dysfunction, including autoimmune thyroiditis, goiter, hypothyroidism, and hyperthyroidism (33, 34). Clinical studies are needed to establish whether current recommendations for safe upper limits on chronic iodine intake are adequate to protect population subgroups at risk for thyroid dysfunction, including older adults.

Materials, tools, and other resources for assessing iodine status and thyroid function

Development of subgroup-specific biological sample pools

There is a need for biological sample pools of serum and urine from defined subgroups of the US population, particularly pregnant women and lactating women, for use in analytical methods development. Trimester-specific serum samples from pregnant women are currently under development by the National Institute for Standards and Technology (NIST).

Development of reference materials for biological samples

Certified Reference Materials (CRMs) are used to validate analytical measurements and to provide quality assurance by serving as control materials. Standard Reference Materials (SRMs) are CRMs issued by the NIST. The NIST is developing breast-milk SRMs that are valid over a limited range of iodine concentrations, but breast-milk CRMs or SRMs covering a wider range of iodine concentrations will still be needed (35). The NIST is also developing trimester-specific serum CRMs or SRMs that span the full range of results for all serum tests of thyroid function (35).

Thyroglobulin can be measured in dried blood spots (DBSs); because DBSs do not require refrigeration, measuring thyroglobulin in DBSs is especially useful in resource-poor regions (29). The NIST is in the early stages of developing a human blood SRM that can be used for DBS, capillary tube, or microsample analyses.

Standardization and harmonization of thyroid function tests

Standardization ensures traceability to the International System of Units, whereas harmonization ensures traceability to a reference system agreed upon by convention (36). The standardization of TSH measures is challenging because of variability in the commercially available immunoassays, but harmonization should be pursued (37).

Standardization of assays for FT4 is an active project of a committee of the International Federation of Clinical Chemistry and Laboratory Medicine (37). Standardization of assays for free triiodothyronine is also needed. To perform standardization, appropriate reference measurement procedures and CRMs (or SRMs) will be required.

Statistical approaches for improving estimates of iodine deficiency and excess

To improve estimates of the prevalences of iodine deficiency and excess derived from food-consumption surveys, suitable statistical approaches are needed to account for variation in the iodine concentrations of high-iodine foods and in food consumption (11). Likewise, to improve estimates of the prevalences

of iodine deficiency and excess derived from UICs, statistical methods that account for the day-to-day variation in UIC are needed (11, 14).

Materials, tools, and other resources for conducting iodine supplementation studies

Development of reference materials for dietary supplements

The NIST has developed an SRM for multi-element multivitamin supplements with a certified value for iodine (38). A CRM or an SRM for prescription prenatal multimineral multivitamin supplements—with a certified value for iodine—is needed.

Development of point-of-care tests for assessing UIC and thyroid function

Point-of-care tests are designed to be performed in the field or in close proximity to where the patient is receiving care. Development, validation, field testing, and harmonization of point-of-care tests for UIC, TSH, and FT4 are needed. Such tests would be particularly useful for patient care and clinical research in low-resource environments. Additional uses may be found in population survey research and medical settings.

Development of frozen meals with specified iodine content

Protocols for clinical research and medical treatment may call for diets with low or specified iodine content. For example, patients scheduled to receive radioiodine therapy to destroy cancerous thyroid tissue are often requested to switch to a low-iodine diet for 1–2 wk before treatment to boost radioiodine uptake by the thyroid. However, as discussed in a recent review, inadequate patient adherence is a likely explanation for inconclusive findings concerning the effect of such a diet on radioiodine treatment outcomes (39). We anticipate that the commercial availability of frozen, prepared meals with defined, verified iodine content would facilitate patient adherence to a low-iodine diet in research and treatment protocols. To foster acceptability across the culturally and ethnically heterogeneous US population, such meals should encompass a range of dietary preferences and restrictions.

Neurobehavioral development outcomes of maternal hypothyroxinemia in previous studies

There is evidence from clinical and epidemiologic studies to suggest that maternal hypothyroxinemia in early pregnancy (before the development of the fetal thyroid) has a negative effect on neurobehavioral development in the offspring (40). However, it is not clear that all such studies have distinguished hypothyroxinemia (characterized by low serum FT4 and normal serum TSH) from mild hypothyroidism (characterized by low serum FT4 and elevated serum TSH). An evaluation of published studies is needed to distinguish infant and child neurodevelopmental outcomes associated with maternal hypothyroxinemia from those associated with mild maternal hypothyroidism. At the same time, the role of potentially confounding variables, including age at testing and iodine supplementation during the lactation period, should be considered across studies.

In a recent prospective study, the school-aged children of women with either low or high serum FT4 during pregnancy had lower scores on an intelligence test and lower gray matter and cortex volumes (41). If high maternal FT4 has developmental effects similar to those of low maternal FT4, then comparing the neurodevelopmental outcomes of low and high maternal FT4, as in a 2012 case-control study (42), may miss the effects of both. An evaluation of published studies is needed to identify such design issues and to determine whether reinterpretation of results or reanalysis of data might be indicated.

Tools for assessing the effects of prenatal iodine supplementation on neurobehavioral development in infants and toddlers

Evaluation and validation of established tasks for assessing the development of specific neurobehavioral functions in infants and toddlers

Various established tasks for assessing the development of specific neurocognitive domains (e.g., visual attention) and other neurobehavioral functions in infants and toddlers may prove useful for evaluating outcomes of prenatal iodine supplementation. These tasks can provide information about the processes that underlie a specific ability and thus go beyond a developmental norm approach that simply indicates whether a milestone was achieved (43, 44). Formal validation is necessary to the acceptance of such tasks as valid tools for public health research. In addition, there is a need for published materials that describe and evaluate these tasks in terms that are accessible to public health scientists. Broader awareness of such tasks should promote their collaborative use by public health scientists and developmental psychologists in clinical studies.

Development and validation of infant and toddler assessment tools for addition to the NIH Toolbox

The current version of the NIH Toolbox for the Assessment of Neurological and Behavioral Function was designed for individuals aged $\geq$3 y (45). The development and validation of new and existing tools for assessing cognitive, mental, and psychomotor functions in infants and toddlers $<$3 y old—such that they can be incorporated into the NIH Toolbox—would facilitate their use for outcomes assessment in prenatal iodine supplementation studies.

Evaluation, selection, and use of neurobehavioral development tests as outcome measures in clinical trials of prenatal iodine supplementation

Clinical studies to evaluate the sensitivity of infant and toddler neurobehavioral development assessment tools to maternal iodine deficiency

Studies of prenatal iodine supplementation in regions of mild to moderate iodine deficiency have relied on 2 global tests of neurobehavioral development: the Bayley Scales of Infant Development (BSID) and the Brunet-Lézine scale. Collectively, the studies have yielded inconsistent findings with regard to psychomotor development, negative findings with regard to mental development, and no information on the development of specific cognitive functions (43).

There is a need for observational clinical studies comparing the BSID, the Brunet-Lézine scale, and established tasks for assessing the sensitivity of the development of specific neurobehavioral functions (cognitive, mental, and psychomotor)

to mild maternal iodine deficiency in early pregnancy. Sensitivity to maternal iodine supplementation likewise could be evaluated in such studies, which could be performed as add-ons to other clinical studies. Neurobehavioral functions of particular interest, and for which established tasks have been developed, include the following (43, 44): visual attention; memory function (e.g., habituation and dishabituation); gross motor skills, such as balance and locomotion; fine motor skills, such as prehension (i.e., grasp); and other motor skills that involve problem solving and tool use.

Prenatal iodine supplementation trials to assess neurobehavioral development outcomes in infants and toddlers

One or more multicenter clinical trials will be needed to assess the effect of prenatal iodine supplementation on neurobehavioral development outcomes in the offspring of women with mild to moderate iodine deficiency. The accurate assessment of individual iodine status is necessary to the success of such a trial, as is the availability of valid measures of infant neurobehavioral development that are sensitive to mild maternal iodine deficiency (46).

The timing of intervention appears to be important. For example, in one study, supplementation starting at 12–14 wk of gestation was associated with lower scores on subscales of the Brunet-Lézine scale than was supplementation starting at 4–6 wk of gestation (47).

In developed countries, the use of iodine supplements during pregnancy has become widespread, increasing the likelihood that nonsupplemented controls will self-initiate supplement use during the course of a clinical trial (48). Such "crossover" in intervention assignment decreases a study's ability to identify an effect of supplementation and, if undetected, can lead to exposure misclassification. Therefore, the study design should include means for identifying and limiting self-initiated supplement use among controls. The failure of supplemented participants to adhere to the supplement regimen likewise can lead to exposure misclassification. Approaches to limiting exposure misclassification might include frequent surveys of supplement intake in both the supplemented and nonsupplemented groups, frequent measurement of 24-h UIE, and counseling participants about adherence to study protocols.

DISCUSSION

The basic, clinical, translational, and population studies needed to characterize the benefits and risks of iodine supplementation, along with related analyses, evaluations, methods development, and other activities, comprise the research and resource needs proposed in the present article. Ongoing or completed clinical trials and epidemiologic studies can offer well-characterized study participants. In addition, there may be data and biological samples from discontinued or completed studies that can be used. Ancillary studies designed to use the participant, biological sample, and data resources of other studies (including those not concerned with iodine) may provide an efficient, cost-effective means to address some of the research questions described in the present article.

Because infant neurodevelopment is critically dependent on maternal iodine before the development of the fetal thyroid (49), in the United States, where mild to moderate iodine deficiency during pregnancy is emerging (50), women in early pregnancy constitute the population subgroup of greatest concern. Iodine deficiency in nonpregnant women of reproductive age is also of concern because of the possibility of pregnancy. It is also important to ensure that nursing infants receive sufficient iodine from breast milk, although it is not clear that lactating women in the United States are at risk for iodine deficiency (51).

There is insufficient information about the benefits and risks of maternal iodine supplementation in the United States and other regions where mild to moderate iodine deficiency has emerged among pregnant women (52). With regard to benefits, the foremost question from a public health perspective is whether any aspect of neurobehavioral development in the offspring of mildly to moderately iodine-deficient women can be improved by maternal iodine supplementation during pregnancy, the corollary of which is that some aspect of neurobehavioral development can be adversely affected by the degree of mild to moderate iodine deficiency encountered. It is also not known whether a narrowly targeted program of iodine supplementation would successfully reach—before the start of pregnancy—women at the greatest risk for iodine deficiency.

There is likewise insufficient information about the benefits and risks of mandating iodine fortification of table salt in the United States. At present, it is unclear whether the projected benefits would justify the possibly increased risks of thyroid dysfunction and related effects in older adults and in others with high iodine intakes (52).

Ultimately, there will be a need for well-designed trials and other studies to assess the impact of supplementation on neurobehavioral development outcomes in the offspring (46). However, 2 basic information gaps loom ahead of such a study: the development of robust, valid, and convenient biomarkers of individual iodine status (29) and the identification of infant and toddler neurobehavioral development outcomes that are sensitive to mild maternal iodine deficiency during pregnancy and its reversal by supplementation (43, 44).

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