Effect of Iodine Supplementation During Pregnancy on Infant Neurodevelopment at 1 Year of Age

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Iodine is the main constituent of thyroid hormones, which in turn are required for fetal brain development. However, the relation between iodine intake during pregnancy, thyroid function, and child neurodevelopment needs further evaluation. The authors assessed the association of maternal iodine intake from diet and supplements during pregnancy and of maternal and neonatal thyroid function with infant neurodevelopment. The Mental Development Index and Psychomotor Development Index (PDI) for 691 children were obtained between 2005 and 2007 using the Bayley Scales of Infant Development at age 1 year in a prebirth cohort in Valencia, Spain. In multivariate analyses, a maternal thyrotropin level >4 μU/mL was associated with an increased risk of a PDI <85 (odds ratio = 3.5, P = 0.02). Maternal intake of ≥150 μg/day, compared with <100 μg/day, of iodine from supplements was associated with a 5.2-point decrease in PDI (95% confidence interval: −8.1, −2.2) and a 1.8-fold increase in the odds of a PDI <85 (95% confidence interval: 1.0, 3.3). When analyses were stratified by sex, this association was intensified for girls but was not observed for boys. Further evidence on the safety and effectiveness of iodine supplementation during pregnancy is needed before it is systematically recommended in iodine-sufficient or mildly deficient areas.

Abbreviations: CI, confidence interval; INMA, INFancia y Medio Ambiente; PDI, Psychomotor Development Index; TSH, thyroid-stimulating hormone.

Adequate maternal iodine nutrition before and during pregnancy is essential for adjusting thyroid function to the increasing demands of the pregnant condition. Moreover, maternal thyroid hormones, especially during the first half of pregnancy, are crucial for correct maturation of the central nervous system of the fetus and subsequent neurodevelopment of the child (1, 2).

There is widespread evidence regarding the deleterious effects of severe iodine deficiency during pregnancy on both maternal thyroid function and child development (3, 4). Furthermore, overt maternal hypothyroidism has been related to adverse reproductive outcomes and poor developmental achievement in children (5, 6). However, the impact of maternal subtle dysfunctions, such as subclinical hypothyroidism or transient hypothyroxinemia, remains less well established (7–12).

Ideally, women should have sufficient iodine nutrition long before conception; accordingly, universal salt iodization programs are considered the best strategy to prevent neurodevelopment disorders related to iodine deficiency (3, 13). However, a current common practice in developed countries consists of recommending systematic iodine supplementation early in pregnancy, even in areas considered iodine sufficient for the general population, such as the United States (14). The rationale forwarded is that the small risks of iodine excess are outweighed by the substantial hazards of iodine deficiency during pregnancy.
Nevertheless, in recent years, an association has been reported between increased iodine intake and a higher prevalence of subclinical and even overt hypothyroidism in the general population and in women of reproductive age (15–18). Moreover, recent studies of pregnant women from areas of different iodine nutritional status have reported altered maternal thyroid hormone levels to be associated with higher iodine intake from dietary (12) or supplement sources (19) but without correspondingly worse infant neurodevelopment.

Therefore, further evidence is needed about the benefits of iodine supplementation during pregnancy on maternal thyroid function and child development, especially in mildly iodine-deficient or iodine-sufficient populations. Moreover, the role of thyroid markers during pregnancy as predictors of offspring development should be further elucidated because these markers might be used for early detection of women at risk.

As part of the Spanish cohort study INMA (INFancia y Medio Ambiente (Childhood and Environment)) (20), we previously reported an increased risk of raised thyroid-stimulating hormone (TSH) during the first half of pregnancy for women who consumed supplements containing iodine (21). In the current study, we assessed the effect of maternal iodine supplementation during pregnancy on the cognitive and psychomotor development of infants at 1 year of age. Furthermore, we analyzed the relation of maternal and neonatal thyroid hormone levels with infant development.

MATERIALS AND METHODS

Population and study design

We studied children from the INMA project, a Spanish, population-based, mother-and-child, multicenter cohort study (20). In the present analysis, we used data from the INMA-Valencia cohort. Mothers’ recruitment, eligibility criteria, and follow-up during pregnancy are described elsewhere (22). Briefly, 855 women were enrolled during their first prenatal visit to La Fe Hospital in Valencia, Spain, before week 13 of gestation. Between May 2004 and February 2006, 787 pregnant women who continued in the study delivered a live infant. After birth, 5 children died, 69 were withdrawn from the study, and 5 were lost to follow-up, leaving 708 children followed until 1 year of age. In the present study, we included 691 children who were evaluated for neuropsychological development during pregnancy on the cognitive and psychomotor development of infants at 1 year of age. Furthermore, we analyzed the relation of maternal and neonatal thyroid hormone levels with infant development.

Study variables

Maternal and child characteristics were collected using 1) questionnaires completed during the first and third trimesters of pregnancy and when the child was 1 year of age and 2) maternal and infant clinical records. Relevant variables are summarized in Table 1. A widely used Spanish adaptation of the British classification system was used to define socioeconomic status according to the most privileged occupation of the mother or father during pregnancy (23). We estimated fetal growth restriction in weight using a customized model, taking into account parental and newborn variables (24, 25).

Assessment of iodine intake

Usual dietary intake during pregnancy was assessed with a 100-item, semiquantitative food frequency questionnaire administered to pregnant women at 10–13 weeks and at 28–32 weeks. The food frequency questionnaire was an adapted version of the Willett questionnaire (26), previously validated and developed for an adult Spanish population in Valencia (27). The questionnaire included 11 dairy and 11 fish items, the main dietary contributors to iodine intake (28). Mean consumption according to both questionnaires was used to estimate average dairy product and fish intake in grams from the last menstrual period until the third trimester of pregnancy. Additionally, the type of salt consumed and the use of vitamin/mineral preparations containing iodide were collected using a structured questionnaire. Estimated iodine intake from supplements was based on supplement brand name and composition, daily dose, and timing of consumption. Mean supplementary iodine intake during the months of consumption was classified as a mean dose <100 µg/day, 100–149 µg/day, or ≥150 µg/ day (range: 150–356). Iodine intake estimates from different sources and their association with urinary iodine concentration have already been described in our study sample (29).

Biomarker analysis

Maternal blood samples and fasting spot urine samples were collected at the end of the first trimester of pregnancy (mean: 12.4 (standard deviation, 0.66) weeks) and were stored at −80°C and −20°C, respectively, until they were delivered to the reference laboratory (Normative Public Health Laboratory of Bilbao, Basque Country). Serum TSH and free thyroxine were measured by a solid-phase, time-resolved sandwich fluoroimmunoassay (AutoDELFI, PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland) using a lanthanide metal europium label. Urinary iodine concentration was measured using paired-ion, reversed-phase, high-performance liquid chromatography with electrochemical detection and a silver working electrode (30). Neonatal TSH levels were measured in a heel-prick blood sample spotted on filter paper, which is routinely obtained shortly after birth for the national hypothyroidism screening program (mean age: 3.45 (standard deviation, 3.43) days) (31). To define hyperthyrotropinemia, we chose the cutoff value of TSH >4 µU/mL, corresponding approximately to the 98th percentile reported in a large population-based study of pregnant women aimed at establishing gestational-age-specific
reference intervals for TSH during the first and second trimesters of pregnancy (32). Urinary iodine concentration was categorized according to the World Health Organization–recommended normal range for pregnant women (150–249 μg/L) (33).

Neurodevelopmental evaluation

Infant neurodevelopment was evaluated with the Bayley Scales of Infant Development (34), which examine infants’ mental and motor development from 2 months to 30 months of age. The tests were administered by trained psychologists when the infants were about 1 year of age (range: 11–16 months) in La Fe Hospital, Valencia. The Bayley Scales of Infant Development are composed of the Mental Scale (163 items), the Motor Scale (81 items), and the Behavior Scale (30 items). In our analysis, only the Mental and Psychomotor scales were used. Special conditions of infants at the time of testing were registered because they could affect the quality of the Bayley evaluation (e.g., rejecting behaviors, irritability, tiredness, sleepiness, feverish).

Raw scores were adjusted for psychologist and for child’s age at test administration to obtain the Mental Development Index and the Psychomotor Development Index (PDI). Linearity was evaluated using fractional polynomial regression models, and heterogeneity was modeled using generalized least squares. Standardized residuals were typified to a mean of 100 with a standard deviation of 15 points to homogenize the scales.

In the present study, we excluded from the analyses 2 outliers for mental and 2 outliers for psychomotor scores that were more than 4 standard deviations above or below the mean.

Statistical analysis

Linear and logistic regression models were defined for the Mental Development Index and the PDI. In logistic regression models, we considered 1 standard deviation below the mean to identify a slight delay in neurodevelopment. Core models were built following a 2-step procedure. The variables child’s sex, maternal age, and maternal history of thyroid disease were retained in all models. Subsequently,
following a stepwise selection procedure, variables from Table 1 related at \( P < 0.20 \) (analysis of variance/likelihood ratio tests) to the response variable were also included. Finally, 4 multivariate models were built, where the development scores were examined in relation to 1) maternal urinary iodine concentration; 2) maternal iodine intake variables during pregnancy: dairy, seafood, iodized salt, and supplements; 3) maternal thyroid function during the first trimester: TSH and free thyroxine; and 4) neonatal thyroid function: TSH.

In all these models, additional confounders were included if they changed the magnitude of the main effects by >10%. Fetal growth restriction and gestational age at delivery were not included in models 1–3 related to maternal urinary iodine concentration; 2) maternal iodine intake variables during pregnancy: dairy, seafood, iodized salt, and supplements; 3) maternal thyroid function during the first trimester: TSH and free thyroxine; and 4) neonatal thyroid function: TSH.

We tested for plausible interactions between the study variables. On the one hand, we evaluated the presence of sex differences in the effect of iodine and thyroid function on child neurodevelopment based on the results from previous studies conducted in animal experiments (36, 37). On the other hand, we accounted for accumulation of iodine intake, evaluating the interaction between iodine intake from the main sources, that is, supplementation and iodized salt, since deficiency and excess can both negatively affect thyroid function and, subsequently, infant neurodevelopment (33). When interactions were significant at 5%, stratified analyses were carried out.

Additionally, we conducted sensitivity analyses by excluding those cases suspected to increase the residual variability of the model: women with a history of thyroid disease (24 cases), children in treatment for pathologies that could affect infant neurodevelopment (8 cases: 3 hypotonic, 3 with plagiocephalia, 1 shortening of the sternocleidomastoid muscle, and 1 psychomotor delay caused by fetal distress), children with special conditions at the time of the Bayley evaluation (44 cases), or preterm deliveries (34 cases).

Statistical analyses were conducted with Stata 9.0 software (Stata Corporation, College Station, Texas).
RESULTS

Mean age of infants at evaluation was 12.3 (standard deviation, 0.6) months (range: 11.3–16.0). Maternal and infant characteristics and their association with infant neurodevelopment are shown in Table 1. Mental Development Index was related to maternal age, gestational age at delivery, child’s sex, and fetal growth restriction. On the other hand, higher gestational age at delivery, cohabiting with both parents, and nonattendance at a day-care center during the first year of life were related to a better PDI. Social class was also related to PDI. The main differences were found between the intermediate class and the most privileged groups.

We next compared neurodevelopment test scores according to iodine intake and thyroid function variables (Table 2). Intake of supplements containing iodine was the only variable related to neurodevelopment. A pattern was found between the dose of iodine in supplements and PDI: 43.3% of women took a mean dose of 100–149 μg/day during pregnancy, and their children showed a 2.0-point decrease in PDI compared with the children of mothers taking <100 μg/day (24.5%). This difference was greater when mothers took ≥150 μg/day (32.2%), with a decrease of 5.5 points. The associations of maternal and infant covariates with iodine and thyroid function variables are presented in Web Table 1 (the first of 2 Web tables, both posted on the Journal’s Web site (http://aje.oupjournals.org/)). Briefly, TSH >4 mIU/L was associated with higher education and social class and with a history of thyroid disease; fetal growth restriction was related to higher maternal free thyroxine and neonatal TSH levels.

In multivariate linear and logistic analyses, no associations were found between Mental Development Index and iodine and thyroid variables (Web Table 2). PDI results are shown in Table 3. Intake of ≥150 μg/day of supplementary iodine, compared with <100 μg/day, was associated with a decrease in PDI of 5.2 points (95% confidence interval (CI): 2.2, 8.1). A significant interaction (P = 0.01) was found between iodine intake from supplements and sex on the odds of a PDI <85. Intake of ≥150 μg/day of supplementary iodine was associated with a 4.0-fold increase in the odds of a PDI <85 for girls (95%
Table 3. Association of Iodine Intake and Maternal and Neonatal Thyroid Function With PDI in Multiple Linear and Logistic Regression, INMA-Valencia Study, Spain, 2005–2007

<table>
<thead>
<tr>
<th>Continuous PDI</th>
<th>PDI &lt;85</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta^a )</td>
</tr>
<tr>
<td>Model 1: maternal urine (( n = 644 ))</td>
<td></td>
</tr>
<tr>
<td>Urinary iodine concentration, ( \mu g/L )</td>
<td></td>
</tr>
<tr>
<td>(&lt;100)</td>
<td>1.3</td>
</tr>
<tr>
<td>(100–149)</td>
<td>1.1</td>
</tr>
<tr>
<td>(150–249)</td>
<td>Ref</td>
</tr>
<tr>
<td>(\geq 250)</td>
<td>0.3</td>
</tr>
<tr>
<td>Model 2: maternal diet and supplement use during pregnancy</td>
<td></td>
</tr>
<tr>
<td>Combined analysis (( n = 682 ))</td>
<td></td>
</tr>
<tr>
<td>Dairy, per 100 g/day</td>
<td>-0.2</td>
</tr>
<tr>
<td>Seafood, per 100 g/day</td>
<td>-1.5</td>
</tr>
<tr>
<td>Iodized salt consumption</td>
<td>-1.0</td>
</tr>
<tr>
<td>Iodine intake from supplements, ( \mu g/day )</td>
<td>0.002</td>
</tr>
<tr>
<td>(&lt;100)</td>
<td>Ref</td>
</tr>
<tr>
<td>(100–149)</td>
<td>-1.7</td>
</tr>
<tr>
<td>(\geq 150)</td>
<td>-5.2</td>
</tr>
<tr>
<td>Girls (( n = 325 ))</td>
<td></td>
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<tr>
<td>Iodine intake from supplements, ( \mu g/day )</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(&lt;100)</td>
<td>Ref</td>
</tr>
<tr>
<td>(100–149)</td>
<td>-2.9</td>
</tr>
<tr>
<td>(\geq 150)</td>
<td>-8.7</td>
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<tr>
<td>Boys (( n = 357 ))</td>
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<tr>
<td>Iodine intake from supplements, ( \mu g/day )</td>
<td>0.56</td>
</tr>
<tr>
<td>(&lt;100)</td>
<td>Ref</td>
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<tr>
<td>(100–149)</td>
<td>0.1</td>
</tr>
<tr>
<td>(\geq 150)</td>
<td>-1.8</td>
</tr>
<tr>
<td>Model 3: maternal thyroid function (( n = 643 ))</td>
<td></td>
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<tr>
<td>TSH, mlU/L</td>
<td>0.049</td>
</tr>
<tr>
<td>(\leq 4)</td>
<td>Ref</td>
</tr>
<tr>
<td>(&gt;4)</td>
<td>-6.2</td>
</tr>
<tr>
<td>Free thyroxine, pmol/L</td>
<td>-0.4</td>
</tr>
<tr>
<td>Model 4: newborn heel-prick blood sample (( n = 669 ))</td>
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</tr>
<tr>
<td>TSH, mlU/L</td>
<td>0.28</td>
</tr>
<tr>
<td>(\leq 4)</td>
<td>Ref</td>
</tr>
<tr>
<td>(&gt;4)</td>
<td>-3.2</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; INMA, Infancia y Medio Ambiente; OR, odds ratio; PDI, Psychomotor Development Index; Ref, referent; TSH, thyroid-stimulating hormone.

* Estimated coefficients/odds ratios from a model that also includes the variables child’s sex, maternal age, cohabitant, social class, day-care center attendance, and history of thyroid disease.

1 Logistic models also include the variable country of origin.

2 From the \( F \) test in linear regression or from the likelihood ratio test in logistic regression.

3 Stratified analysis by sex (\( P \) for interaction between iodine intake from supplements and sex: on PDI = 0.081 and on logit(PDI < 85) = 0.012). The stratified models do not include the variable cohabitant.

4 Model 4 also includes the variables age at time of blood sampling, gestational age (single and quadratic terms), and fetal growth restriction.
CI: 1.4, 11.4). This pattern was not observed for boys, and, in contrast, a significantly lower risk of a PDI <85 was observed in the 100–149 µg/day group compared with the <100 µg/day group (odds ratio = 0.4, 95% CI: 0.2, 0.9). In multivariate analysis, the starting time of supplement intake (early vs. intermediate/late pregnancy, defined as before or after the end of the first trimester of pregnancy), was not associated with neurodevelopment (data not shown). Moreover, inclusion of gestational age and fetal growth restriction in models 1–3 did not substantially alter these results.

Maternal thyroid function was also related to PDI but with no significant interaction by sex. TSH levels >4 mIU/L were related to an increased risk of a PDI <85 (odds ratio = 3.5, 95% CI: 1.3, 9.5) and a decrease in PDI score (−6.2, 95% CI: −12.3, 0.0).

Sensitivity analyses showed no major alterations in the associations related to iodine supplementation. However, exclusion of women with a history of thyroid disease led to nonsignificant associations between maternal TSH and PDI (β = −4.9, 95% CI: −11.6, 1.8; odds ratio = 2.6, 95% CI: 0.9, 7.9).

DISCUSSION

We examined the relation of maternal iodine intake and biochemical markers of thyroid function during pregnancy with infant neurodevelopment at 1 year of age. Maternal urinary iodine concentration, iodized salt consumption, or dietary intake of foods with a high iodine content was not associated with infant neurodevelopment. However, maternal intake of ≥150 µg/day of an iodine supplement was associated with a 5.2-point decrease in PDI and with a 1.8-fold increase in the odds of a PDI <85. When analyses were stratified by sex, this association was intensified for girls, while it was not observed for boys. Maternal hyperthyrotropinemia (TSH >4 mIU/L) at the end of the first trimester of pregnancy was the only thyroid biomarker associated with poorer psychomotor achievement.

As far as we know, this study is the first reported to date in which maternal consumption of multivitamins containing iodine during pregnancy was related to lower psychomotor achievement in infants. Moreover, we observed gender differences in the deleterious effects of iodine supplements on neurodevelopment, with an association for females but not for males. A protective effect was found for boys in the intermediate supplement dose category, but this result should be considered with caution given the absence of a consistent result in the continuous analysis.

While the beneficial effects of iodine supplementation during pregnancy on child neurodevelopment have been widely documented in severely iodine-deficient areas (4, 38), few studies have analyzed this effect in mildly iodine-deficient (19, 39) or iodine-sufficient (11) populations. Berbel et al. (39) reported, in a trial carried out in a mildly iodine-deficient area of Spain, better developmental scores for children whose mothers took supplements beginning in early pregnancy compared with those starting supplementati-
potassium iodide supplements. Because multivitamins include many other vitamin and mineral compounds apart from iodine, we could not ascertain whether the association we found may be due to only their iodine content or to other compounds, too.

Although we adjusted for a wide range of potential confounding effects, it is possible that women who consumed supplements during pregnancy also had some negative clinical or psychosocial conditions not accounted for that might explain the poorer developmental achievement of their offspring. However, reverse-causation bias is unlikely because multivitamins are given as part of common and extended antenatal care, and hence supplement prescription and dose were not determined by specific women’s conditions. Moreover, no association was found between the maternal or child covariates and consumption of multivitamins containing iodine, although other potential confounders not accounted for cannot be discarded. Among them, we could not measure thyroid antibodies, which might have helped to further explain the observed effect of supplement intake on thyroid dysfunction and child development.

Strengths of the present study include the wide range of iodine intake variables and thyroid status biomarkers assessed, as well as confounding variables we accounted for. The consistency of the associations between supplement intake and elevated TSH (21), and between both factors with child psychomotor development, supports the relation found. Moreover, some evidence based on animal experiments (36, 37) may explain, at least in part, the biologic pathways of the specific gender effect observed. The prospective design of the INMA study will provide us with the opportunity to determine the long-term effects of supplementation and maternal thyroid function during pregnancy in future psychological evaluations.

In summary, this is the first known report of a potentially deleterious effect of maternal consumption of multivitamins containing iodine during pregnancy on psychomotor achievement in infants, specifically in girls; therefore, these results should be evaluated with caution. Incipient evidence is already available regarding the link between supplementary (19, 21) or excessive (12) iodine intake and indicators of thyroid dysfunction during pregnancy in mildly iodine deficient or iodine-sufficient populations. Further evidence on the safety and long-term effectiveness of iodine supplementation is needed before it is systematically recommended during pregnancy. At the same time, more effort should be devoted to improving basal iodine nutrition status in the population, by strengthening universal salt iodization programs through political and industry commitment, to assure adequate iodine intake long before pregnancy.

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A full list of the INMA Project researches can be found at the following Web site: http://www.proyectoinma.org.

Conflict of interest: None declared.

REFERENCES


