American Journal of Epidemiology

Vol. 173, No. 7
DOI: 10.1093/aje/kwq424
Advance Access publication:
March 8, 2011

Original Contribution

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

Mario Murcia*, Marisa Rebagliato, Carmen Iñiguez, Maria-Jose Lopez-Espinosa, Marisa Estarlich, Belén Plaza, Carmen Barona-Vilar, Mercedes Espada, Jesús Vioque, and Ferran Ballester

* Correspondence to Mario Murcia, Unit of Environment and Health, Centre for Public Health Research (CSISP), Avda Catalunya 21, 46020 Valencia, Spain (e-mail: murcia_mar@gva.es).

Initially submitted June 8, 2010; accepted for publication November 5, 2010.

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.

child development; dietary supplements; fetal development; iodine; prenatal nutritional physiological phenomena; thyroid hormones

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 between June 2005 and February 2007, before 18 months of age. Four children were excluded because they were evaluated at older ages, 8 because of an incomplete neuropsychological assessment, and 5 because of specific clinical conditions (2 very preterm, 1 Down syndrome, 1 epilepsy, and 1 autistic disorder). All participating women gave their written informed consent, and the study was approved by the Ethics Committee of La Fe Hospital.

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 iodine 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 (AutoDELFIA, 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

Table 1. Characteristics of the Study Population and Their Association With Infant Neurodevelopment, INMA-Valencia Study, Spain, 2005–2007

	No.	%	Mental Development Index		Psychomotor Development Index	
			Mean (SD)	*P* Value[a]	Mean (SD)	*P* Value[a]
Maternal characteristics						
Country of origin				0.88		0.47
Spain	608	88.0	100.0 (15.3)		99.8 (15.0)	
Other	83	12.0	100.2 (12.5)		101.1 (15.4)	
Educational level				0.69		0.34
Up to primary school	217	31.4	100.7 (15.8)		101.2 (15.7)	
Secondary school	299	43.3	99.7 (15.0)		99.5 (15.0)	
University degree	175	25.3	99.6 (14.1)		99.4 (14.1)	
Social class				0.45		0.050
I + II (highest)	161	23.3	100.5 (14.0)		101.7 (13.9)	
III	190	27.5	98.8 (15.8)		97.9 (14.7)	
IV + V (lowest)	340	49.2	100.4 (15.0)		100.4 (15.6)	
Cohabitant				0.84		0.021
Baby's father	673	98.1	99.9 (15.1)		100.2 (14.7)	
Others	13	1.9	100.8 (14.7)		90.5 (21.9)	
Employed at baby's age 1 year				0.83		0.52
No	285	41.6	99.8 (14.8)		100.5 (15.3)	
Yes	400	58.4	100.1 (15.3)		99.7 (14.7)	
Smoking				0.81		0.20
Not during pregnancy	417	60.7	99.7 (15.1)		100.8 (15.0)	
During pregnancy, not at present	83	12.1	99.9 (15.8)		97.9 (16.2)	
During pregnancy and at present	187	27.2	100.6 (14.6)		99.4 (14.4)	
History of thyroid disease				0.63		0.089
No	667	96.5	100.1 (15.1)		100.2 (15.1)	
Yes	24	3.5	98.6 (12.5)		94.9 (10.6)	

Table continues

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,

Table 1. Continued

	No.	%	Mental Development Index		Psychomotor Development Index	
			Mean (SD)	*P* Value[a]	Mean (SD)	*P* Value[a]
		Mean (SD)	β (SE)		β (SE)	
Age, years	691	30.1 (4.4)	−0.46 (0.13)	<0.001	−0.24 (0.13)	0.063
		%	Mean (SD)		Mean (SD)	
Infant characteristics						
Sex				0.001		0.18
Girl	328	47.5	102.0 (13.9)		100.8 (15.1)	
Boy	363	52.5	98.2 (15.7)		99.3 (14.9)	
Breastfeeding, weeks				0.71		0.59
<2	148	21.4	99.8 (16.1)		100.8 (15.4)	
2–15.9	142	20.5	98.8 (13.5)		101.1 (14.2)	
16–24	100	14.5	100.9 (16.3)		99.3 (16.1)	
>24	301	43.6	100.3 (14.7)		97.7 (13.2)	
Day-care center attendance				0.11		0.039
No	542	79.0	100.4 (14.6)		100.6 (14.7)	
Yes	144	21.0	98.2 (16.5)		97.7 (15.5)	
Perinatal outcomes						
Fetal growth restriction				0.011		0.49
No	616	89.3	100.5 (14.7)		100.1 (14.8)	
Yes	74	10.7	95.8 (17.0)		98.9 (16.7)	
		Median (IQR)	β (SE)		β (SE)	
Gestational weeks at delivery	691	39.9 (38.9–40.6)	2.38 (0.37)	<0.001	1.51 (0.38)	<0.001

Abbreviations: INMA, INfancia y Medio Ambiente; IQR, interquartile range; SD, standard deviation; SE, standard error.
[a] From analysis of variance test (categorical variables) or linear regression (continuous variables).

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 iodine intake and thyroid status since, on theoretical grounds, they were considered potential mediators. In this case, adjustment for fetal growth restriction and gestational age at delivery could provoke an attenuation of the estimate because the effect mediated was eliminated, and even in a bias situation (35). In the case of neonatal TSH (model 4), both variables were adjusted for since they confounded the association and were less plausibly on the causal pathway.

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).

Table 2. Iodine Intake Variables, Maternal and Neonatal Thyroid Function, and Their Association With Children's Neurodevelopment, INMA-Valencia Study, Spain, 2005–2007

			Mental Development Index		Psychomotor Development Index	
	No.	%	Mean (SD)	*P* Value[a]	Mean (SD)	*P* Value[a]
Urinary iodine concentration, μg/L				0.50		0.68
<100	220	33.9	100.0 (13.3)		100.7 (14.7)	
100–149	137	21.1	101.0 (15.7)		100.8 (14.4)	
150–249	165	25.4	98.4 (16.0)		99.4 (15.2)	
≥250	127	19.6	100.2 (14.5)		99.3 (13.6)	
Iodized salt consumption				0.70		0.44
No	251	36.3	100.3 (15.0)		100.6 (14.9)	
Yes	440	63.7	99.8 (15.0)		99.7 (15.1)	
Iodine intake from supplements, μg/day				0.76		0.001
None or <100	169	24.5	100.7 (15.1)		102.6 (15.1)	
Mean: 100–149	298	43.3	99.8 (13.8)		100.6 (14.3)	
Mean: ≥150	222	32.2	99.6 (16.5)		97.1 (15.5)	
Maternal TSH, μU/mL				0.19		0.098
≤4	624	96.3	100.0 (14.8)		100.4 (14.9)	
>4	24	3.7	104.0 (13.5)		95.3 (13.8)	
Neonatal TSH, μU/mL				0.17		0.13
≤4	652	95.9	100.2 (14.9)		100.3 (15.0)	
>4	28	4.1	96.2 (17.0)		95.8 (15.4)	
		Median (IQR)	β (SE)		β (SE)	
Dairy intake during pregnancy, per 100 g/day	691	4.8 (3.3–6.4)	−0.06 (0.26)	0.81	−0.28 (0.26)	0.28
Seafood intake during pregnancy, per 100 g/day	691	0.65 (0.45–0.90)	−0.88 (1.67)	0.60	−2.79 (1.66)	0.094
Maternal free thyroxine, pmol/L	648	10.9 (10.1–11.9)	−0.36 (0.40)	0.36	−0.32 (0.40)	0.42

Abbreviations: INMA, INfancia y Medio Ambiente; IQR, interquartile range; SD, standard deviation; SE, standard error; TSH, thyroid-stimulating hormone.

[a] From analysis of variance test (categorical variables) or linear regression (continuous variables).

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

	Continuous			PDI <85		
	β[a]	95% CI	*P* Value[c]	OR[a,b]	95% CI	*P* Value[c]
Model 1: maternal urine ($n = 644$)						
Urinary iodine concentration, μg/L			0.81			0.98
<100	1.3	−1.6, 4.2		0.9	0.5, 1.6	
100–149	1.1	−2.2, 4.4		0.9	0.5, 1.7	
150–249	Ref			Ref		
≥250	0.3	−3.1, 3.6		0.9	0.5, 1.7	
Model 2: maternal diet and supplement use during pregnancy						
Combined analysis ($n = 682$)						
Dairy, per 100 g/day	−0.2	−0.7, 0.3	0.49	1.0	0.9, 1.1	0.86
Seafood, per 100 g/day	−1.5	−4.8, 1.8	0.38	1.1	0.6, 2.0	0.85
Iodized salt consumption	−1.0	−3.3, 1.3	0.40	1.0	0.6, 1.5	0.87
Iodine intake from supplements, μg/day			0.002			0.013
<100	Ref			Ref		
100–149	−1.7	−4.4, 1.1		0.9	0.5, 1.6	
≥150	−5.2	−8.1, −2.2		1.8	1.0, 3.3	
Girls ($n = 325$)[d]						
Iodine intake from supplements, μg/day			<0.001			0.017
<100	Ref			Ref		
100–149	−2.9	−6.8, 1.0		2.5	0.9, 7.0	
≥150	−8.7	−13.0, -4.4		4.0	1.4, 11.4	
Boys ($n = 357$)[d]						
Iodine intake from supplements, μg/day			0.56			0.013
<100	Ref			Ref		
100–149	0.1	−3.9, 4.1		0.4	0.2, 0.9	
≥150	−1.8	−6.0, 2.5		1.1	0.5, 2.2	
Model 3: maternal thyroid function ($n = 643$)						
TSH, mIU/L			0.049			0.021
≤4	Ref			Ref		
>4	−6.2	−12.3, 0.0		3.5	1.3, 9.5	
Free thyroxine, pmol/L	−0.4	−1.2, 0.3	0.27	1.1	0.9, 1.2	0.48
Model 4: newborn heel-prick blood sample ($n = 669$)[e]						
TSH, mIU/L			0.28			0.51
≤4	Ref			Ref		
>4	−3.2	−8.9, 2.6		1.4	0.5, 3.7	

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

[a] 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.

[b] Logistic models also include the variable country of origin.

[c] From the *F* test in linear regression or from the likelihood ratio test in logistic regression.

[d] 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.

[e] 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 difference 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 supplementation later or only after delivery. Neurodevelopment was evaluated at 18 months of age in 44 selected children only: in the group with the earliest supplementation, only those children whose mothers had normal thyroid function at the beginning of gestation and at full term were selected; in the other 2 groups, children selected were born either to hypothyroxinemic women during the first trimester or at full term. Therefore, this study design may enable evaluation of maternal hypothyroxinemia at different points in time during gestation, but it is not suitable for assessing iodine supplementation.

Velasco et al. (19) also reported, in a Spanish area of mild iodine deficiency, that infants of mothers who had received oral 300-μg iodine supplements daily starting with the first trimester of pregnancy and lactation had higher Bayley Psychomotor Development scores than those of mothers who did not take supplements. These results, however, should be considered with caution given the lack of control for confounding variables and the different ages at which infants from the intervention and control groups were evaluated (means: 5.57 months and 12.44 months, respectively).

A prospective cohort study, Project Viva, carried out in an iodine-sufficient area of the United States, did not find a relation between iodine-containing vitamin intake during pregnancy and cognitive test scores at ages 6 months and 3 years (11). However, the proportion of supplement consumers was low (7.7%) compared with that in our study population.

Scant evidence is available regarding gender differences about the importance of iodine or maternal thyroid function for brain development. At least 2 supplementation trials in schoolchildren from iodine-deficient areas found cognitive improvements only or that they were more prominent among girls (40, 41). Animal experiments have provided better support for gender differences in prenatal sensitivity to the effects of maternal thyroid deprivation on neurodevelopment (36, 37, 42). Friedhoff et al. (36) found a gender difference in the effects of restricting maternal thyroid hormone in utero on postnatal learning in rats, with higher sensitivity in females. Chan et al. (37) provided further evidence of the biologic pathways in an experiment of gene expression in nutrient-deprived fetal guinea pigs. These authors observed a gender-specific fetal brain mRNA expression of nuclear thyroid hormone receptors that suggested a greater male than female potential to compensate for lower maternal thyroid transfers.

The association observed in our study between elevated maternal TSH in early pregnancy and poorer psychomotor development agrees with previous reported studies by Haddow et al. in the United States (7) and by Li et al. in China (10). This subtle maternal thyroid dysfunction was already reported to be related to maternal iodine supplementation in our study sample (21); therefore, it might be one of the intermediate mechanisms to explain the deleterious effect of iodine-containing multivitamins on infant neurodevelopment. However, we did not observe any association of maternal free thyroxine with child neurodevelopmental outcomes, agreeing with the Project Viva results (11) but not with those of other studies (8–10, 43).

Our study presents several limitations. All women consumed iodine-containing multivitamins and not specific

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.

ACKNOWLEDGMENTS

Author affiliations: Spanish Consortium for Research on Epidemiology and Public Health (CIBERESP), Barcelona, Spain (Mario Murcia, Marisa Rebagliato, Carmen Iñiguez, Maria-Jose Lopez-Espinosa, Marisa Estarlich, Belén Plaza, Jesús Vioque, Ferran Ballester); Unit of Environment and Health, Centre for Public Health Research (CSISP), Valencia, Spain (Mario Murcia, Marisa Rebagliato, Carmen Iñiguez, Marisa Estarlich, Ferran Ballester); Department of Social and Environmental Health Research, London School of Hygiene and Tropical Medicine, London, United Kingdom (Maria-Jose Lopez-Espinosa); Public Health Board, Conselleria de Sanitat, Valencia, Spain (Marisa Rebagliato, Carmen Barona-Vilar); Clinical Chemistry Unit, Public Health Laboratory of Bilbao, Bilbao, Spain (Mercedes Espada); Department of Public Health, Miguel Hernández University, Alicante, Spain (Jesús Vioque); Department of Nursing, University of Valencia, Valencia, Spain (Ferran Ballester).

This work was supported by grants from Instituto de Salud Carlos III (Red INMA G03/176 and CB06/02/0041), the Spanish Ministry of Health (FIS 03/1615, FIS 04/1509, FIS 04/1436, FIS 05/1079, FIS 06/1213, FIS 06/0867, FIS 09/02647), Conselleria de Sanitat - Generalitat Valenciana (048/2010), and Fundació Roger Torné.

The authors thank Amparo Cases, Amparo Quiles, Eva Navarrete, and Maria Dolores Climent-Barber for their support with the fieldwork and the collection and processing of nutritional data.

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

1. de Escobar GM, Obregón MJ, del Rey FE. Maternal thyroid hormones early in pregnancy and fetal brain development. *Best Pract Res Clin Endocrinol Metab.* 2004;18(2):225–248.
2. de Escobar GM, Obregón MJ, del Rey FE. Iodine deficiency and brain development in the first half of pregnancy. *Public Health Nutr.* 2007;10(12A):1554–1570.
3. Glinoer D. The importance of iodine nutrition during pregnancy. *Public Health Nutr.* 2007;10(12A):1542–1546.
4. Zimmermann MB. Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review. *Am J Clin Nutr.* 2009;89(2):668S–672S.
5. Klein RZ, Mitchell ML. Maternal hypothyroidism and child development. A review. *Horm Res.* 1999;52(2):55–59.
6. Casey BM, Leveno KJ. Thyroid disease in pregnancy. *Obstet Gynecol*. 2006;108(5):1283–1292.
7. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*. 1999;341(8):549–555.
8. Pop VJ, Kuijpens JL, van Baar AL, et al. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clin Endocrinol (Oxf)*. 1999;50(2):149–155.
9. Pop VJ, Brouwers EP, Vader HL, et al. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clin Endocrinol (Oxf)*. 2003;59(3):282–288.
10. Li Y, Shan Z, Teng W, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological

development of their children at 25–30 months. *Clin Endocrinol (Oxf)*. 2010;72(6):825–829.
11. Oken E, Braverman LE, Platek D, et al. Neonatal thyroxine, maternal thyroid function, and child cognition. *J Clin Endocrinol Metab*. 2009;94(2):497–503.
12. Orito Y, Oku H, Kubota S, et al. Thyroid function in early pregnancy in Japanese healthy women: relation to urinary iodine excretion, emesis, and fetal and child development. *J Clin Endocrinol Metab*. 2009;94(5): 1683–1688.
13. Secretariat WHO, Andersson M, de Benoist B, et al. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. *Public Health Nutr*. 2007;10(12A):1606–1611.
14. Public Health Committee of the American Thyroid Association, Becker DV, Braverman LE, et al. Iodine supplementation for pregnancy and lactation—United States and Canada: recommendations of the American Thyroid Association. *Thyroid*. 2006;16(10):949–951.
15. Laurberg P. Global or Gaelic epidemic of hypothyroidism? *Lancet*. 2005;365(9461):738–740.
16. Teng W, Shan Z, Teng X, et al. Effect of iodine intake on thyroid diseases in China. *N Engl J Med*. 2006;354(26):2783–2793.
17. Pedersen IB, Laurberg P, Knudsen N, et al. An increased incidence of overt hypothyroidism after iodine fortification of salt in Denmark: a prospective population study. *J Clin Endocrinol Metab*. 2007;92(8):3122–3127.
18. Vanderver GB, Engel A, Lamm S. Cigarette smoking and iodine as hypothyroxinemic stressors in U.S. women of childbearing age: a NHANES III analysis. *Thyroid*. 2007; 17(8):741–746.
19. Velasco I, Carreira M, Santiago P, et al. Effect of iodine prophylaxis during pregnancy on neurocognitive development of children during the first two years of life. *J Clin Endocrinol Metab*. 2009;94(9):3234–3241.
20. Ribas-Fitó N, Ramón R, Ballester F, et al. Child health and the environment: the INMA Spanish Study. *Paediatr Perinat Epidemiol*. 2006;20(5):403–410.
21. Rebagliato M, Murcia M, Espada M, et al. Iodine intake and maternal thyroid function during pregnancy. *Epidemiology*. 2010;21(1):62–69.
22. Ramón R, Ballester F, Iñiguez C, et al. Vegetable but not fruit intake during pregnancy is associated with newborn anthropometric measures. *J Nutr*. 2009;139(3):561–567.
23. Domingo-Salvany A, Regidor E, Alonso J, et al. Proposal for a social class measure. Working Group of the Spanish Society of Epidemiology and the Spanish Society of Family and Community Medicine [in Spanish]. *Aten Primaria*. 2000; 25(5):350–363.
24. Mamelle N, Cochet V, Claris O. Definition of fetal growth restriction according to constitutional growth potential. *Biol Neonate*. 2001;80(4):277–285.
25. Rodríguez-Bernal CL, Rebagliato M, Iñiguez C, et al. Diet quality in early pregnancy and its effects on fetal growth outcomes: the Infancia y Medio Ambiente (Childhood and Environment) Mother and Child Cohort Study in Spain. *Am J Clin Nutr*. 2010;91(6):1659–1666.
26. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122(1):51–65.
27. Vioque J, Gonzalez L. Validity of a food frequency questionnaire (preliminary results). *Eur J Cancer Prev*. 1991;1(suppl 1):19–20.
28. Brantsaeter AL, Haugen M, Julshamn K, et al. Evaluation of urinary iodine excretion as a biomarker for intake of milk and dairy products in pregnant women in the Norwegian Mother and Child Cohort Study (MoBa). *Eur J Clin Nutr*. 2009; 63(3):347–354.
29. Murcia M, Rebagliato M, Espada M, et al. Iodine intake in a population of pregnant women. INMA mother and child cohort study, Spain. *J Epidemiol Community Health*. 2010; 64(12):1094–1099.
30. Espada M, Marzana I, Unceta M. Assessment of a method for urinary iodine determination using high performance liquid chromatography [in Spanish]. *Química Clínica*. 2000; 19(5):380–383.
31. Barona-Vilar C, Mas-Pons R, Fullana-Montoro A. Neonatal thyrotropinemia (TSH) as an indicator of iodine nutritional level in Castellon and Valencia, Spain (2004–2006) [in Spanish]. *Rev Esp Salud Publica*. 2008;82(4):405–413.
32. Haddow JE, Knight GJ, Palomaki GE, et al. The reference range and within-person variability of thyroid stimulating hormone during the first and second trimesters of pregnancy. *J Med Screen*. 2004;11(4):170–174.
33. World Health Organization, United Nations Children's Fund, International Council for the Control of Iodine Deficiency Disorders. *Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination. A Guide for Programme Managers*. Geneva, Switzerland: World Health Organization; 2007.
34. Bayley N. *The Bayley Scales of Infant Development*. New York, NY: Psychological Corporation; 1969.
35. Hernán MA, Hernández-Díaz S, Werler MM, et al. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *Am J Epidemiol*. 2002;155(2):176–184.
36. Friedhoff AJ, Miller JC, Armour M, et al. Role of maternal biochemistry in fetal brain development: effect of maternal thyroidectomy on behaviour and biogenic amine metabolism in rat progeny. *Int J Neuropsychopharmacol*. 2000;3(2):89–97.
37. Chan SY, Andrews MH, Lingas R, et al. Maternal nutrient deprivation induces sex-specific changes in thyroid hormone receptor and deiodinase expression in the fetal guinea pig brain. *J Physiol*. 2005;566(pt 2):467–480.
38. Qian M, Wang D, Watkins WE, et al. The effects of iodine on intelligence in children: a meta-analysis of studies conducted in China. *Asia Pac J Clin Nutr*. 2005;14(1):32–42.
39. Berbel P, Mestre JL, Santamaría A, et al. Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. *Thyroid*. 2009;19(5):511–519.
40. Bautista A, Barker PA, Dunn JT, et al. The effects of oral iodized oil on intelligence, thyroid status, and somatic growth in school-age children from an area of endemic goiter. *Am J Clin Nutr*. 1982;35(1):127–134.
41. Dodge PR, Palkes H, Fierro-Benitez R, et al. Effect on intelligence of iodine in oil administered to young Andean children—a preliminary report. In: Stanbury JB, ed. *Endemic Goiter*. Washington, DC: Pan American Health Organization; 1969:378–380.
42. Zoeller RT, Rovet J. Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. *J Neuroendocrinol*. 2004;16(10):809–818.
43. Kooistra L, Crawford S, van Baar AL, et al. Neonatal effects of maternal hypothyroxinemia during early pregnancy. *Pediatrics*. 2006;117(1):161–167.