Effect of Iodine Prophylaxis during Pregnancy on Neurocognitive Development of Children during the First Two Years of Life

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Context: The association between thyroid function during pregnancy and the later mental and psychomotor development of the child is supported by numerous experimental, clinical, and epidemiological studies.

Objective: The aim of the study was to evaluate the psychological development of infants aged 3 to 18 months whose mothers had received 300 μg of potassium iodide during the first trimester of their pregnancy and compare with infants whose mothers had received no iodine supplements.

Design and Study Subjects: The study included 133 women who had received 300 μg of potassium iodine and 61 women who had received no iodine supplements.

Main Outcome Measures: The neuropsychological status of the children was evaluated with the Bayley Scales of Infant Development, and measurements were made of TSH, free T_3, free T_4, and urinary iodine.

Results: Those children whose mothers had received an iodine supplement of 300 μg had a more favorable psychometric assessment than those of the other group of mothers. They had higher scores on the Psychomotor Development Index ($P = 0.02$) and the Behavior Rating Scale.

Conclusions: Dietary iodine supplements not only have no harmful effect on the neurodevelopment of the children, they may even be beneficial. Given the possible presence of confounding variables not controlled for in this study, these findings should be considered as preliminary. **(*J Clin Endocrinol Metab* 94: 3234–3241, 2009)**

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Abbreviations: BRS, Behavior Rating Scale; CV, coefficient of variation; FT3, free T_3; FT4, free T_4; MDI, Mental Development Index; OR, odds ratio; PDI, Psychomotor Development Index.

Experimental, clinical, and epidemiological evidence all show the association between thyroid function during pregnancy and infancy and psychological development in children (1, 2). The most common cause of hypothyroxinemia with normal TSH during pregnancy is iodine deficiency (3). Over half the population of Europe live in areas of iodine deficiency (4). The problems related to iodine deficiency and the policies concerning the protection of an adequate iodine intake are far from being resolved (5). Women with an adequate intake of iodine before and during pregnancy have a sufficient amount of iodine stored in the thyroid gland and have no difficulty adapting to the increased demand of the thyroid hormones during pregnancy (6). However, in areas with a mild or moderate iodine deficiency the total amount of stored iodine, reflected by urinary iodine excretion, falls gradually from the first to the third trimester (7).

Several randomized trials have evaluated the impact of iodine intake on the cognitive performance or motor competence of children (1, 8–10). Most, but not all, found an association between a lower intake of iodine and lower levels of free T_4 (FT4) and a deficit in the cognitive or psychomotor development of children. However, the results of these studies are not conclusive because there was great variation in their design, methods, criteria, and exposure period, as well as the psychometric evaluation procedures used. However, as far as we are aware, no study has yet undertaken a programmed intervention with 300 μg of potassium iodine to evaluate its effect on the neuropsychological development of children.

The aim of this study was to evaluate the effect on the cognitive and psychomotor development of infants aged 3–18 months of 300 μg of iodine, in the form of potassium iodine, given to the mothers of these children from the first trimester of pregnancy.

Subjects and Methods

The study was undertaken in 194 pregnant women from the Hospital de la Merced in Osuna, in Andalusia, southern Spain. Women with known thyroid disease or thyroid disease detected during the study were excluded. A total of 133 consecutive women were given 300 μg of iodine (in the form of potassium iodine) from the first trimester of pregnancy (the "300 group"). In this group, 76.9% of the women started before wk 10, and the others started after wk 10 but still within the first trimester. The women continued taking the same dose during lactation.

A control group was composed of 61 women who attended during the last month of pregnancy and who had not received iodine supplements. In addition, urinary iodine was measured in another 31 women who attended the Osuna Hospital because of miscarriage between wk 8 and 12, before performing dilatation and curettage.

The women were followed up with an obstetric history, and measurements were made of TSH, free T_3 (FT3), FT4, thyroglobulin, and urinary iodine concentrations from a casual sample of urine in each of the three trimesters of pregnancy in the 300 group and in the last trimester in the control group. Urinary iodine measurements were also made in 30 newborns from the control group and 75 newborns from the 300 group. The iodine concentration in maternal milk was measured during the immediate postpartum period in 21 mothers from the control group and 67 mothers from the 300 group. Data were recorded on the TSH values from the umbilical cords of all the infants, measured during screening for the early detection of congenital hypothyroidism (11).

All the women gave their informed consent, and the study was reviewed and approved by the Ethics and Research Committee of Carlos Haya University Hospital (Malaga, Spain).

Neurodevelopmental evaluation of the children

The children were evaluated at a single session in the presence of the mother or father. The psychological evaluation was performed by an independent researcher who was unaware of the design sequence of the study. This evaluation was carried out using two procedures: 1) a structured interview of the mother or father to collect sociodemographic data; and 2) the Bayley Scales of Infant Development (12) to measure the development of the child. The Bayley Scales of Infant Development is specific for children aged 2 to 30 months and consists of three scales: the Mental Development Scale, the Psychomotor Development Scale, and the Behavior Rating Scale (BRS). The BRS was done immediately after the other scales.

The Mental Development Scale and the Pychomotor Development Scale are quantitative scales that transform the direct scores obtained in each scale according to age into a Mental Development Index (MDI) and a Psychomotor Development Index (PDI), respectively. The scores obtained are typical normalized scores (100 ± 16). The MDI evaluates sensory/perceptual acuities, the ability to respond to stimuli, object constancy, verbal communication, problem-solving ability, and early generalization and classification ability. The PDI evaluates the child's body control, motor coordination and manipulation skills. The BRS is observational and qualitative and evaluates the child's social orientation and awareness. Because the BRS scores are expressed according to the mode for each age group, a dichotomous variable was established for the statistical analysis that was standardized according to whether the value for each item was lower or higher (the same or higher) than the mode of the item.

Procedures

The TSH, FT3, and FT4 were measured by chemiluminescence (Roche Diagnostics, Basel, Switzerland). For TSH, the detection range is 0.011–200 mIU/liter, and the low, medium, and high coefficient of variation (CV) values were 7.2, 4.5, and 4.1%; for FT4, the detection range is 1.3–155 pmol/liter, and the low, medium, and high CV values were 8, 7.5, and 8%; for FT3, the detection range is 0.8–30.8 pmol/liter, and the low, medium, and high CV values were 10, 5, and 1.9%. The thyroglobulin was measured by immunoradiometric assays in nanograms per milliliter (Dynotest; BRAHMS Diagnostica GmbH, Berlin, Germany). The iodine concentration in urine samples was measured by the modified Benotti and Benotti technique (13). Umbilical

cord human TSH has been measured in blood specimens dried on filter paper by a solid-phase, two-site fluoroimmunometric assay (AutoDELFIA Neonatal hTSH; Perkin-Elmer, Zaventem, Belgium) using the 1235 AutoDELFIA (Perkin-Elmer). Intraassay variation (%CV) was 6.1% (low value) and 5.2% (high value). Interassay variation (% CV) was 9.0% (low value) and 6.7% (high value).

Statistical study

The data are presented as the mean, SD, and proportions. The hypothesis contrast for two samples was made with the Student *t* test or two-way ANOVA. The *post hoc* analysis was done with Duncan's new multiple range test. The strength of the association between variables was measured by calculating the odds ratio (OR) from models of multivariate logistic regression. In all cases, the level of rejection of a null hypothesis was an $\alpha \leq 0.05$ for two tails.

Because the Ethics Committee of Carlos Haya University Hospital did not authorize the inclusion of a control group without treatment, the control group was therefore selected from among those women who attended the Osuna Hospital at the end of their pregnancy who had not been prescribed potassium iodine or any other iodine-enriched supplement.

Results

Sample characteristics

The age at which the children were studied and the number of weeks gestation of the mothers were significantly lower in the 300 group (Table 1).

TABLE 1. Selected demographic and clinical characteristics

	Control group	300 group	*P* value
n	61	133	
Age (months)	12.44 ± 4.96	5.47 ± 2.86	<0.001
Sex (M/F)	34/27	74/59	n.s.
Birth weight (kg)	3.34 ± 0.36	3.25 ± 0.54	n.s.
Length of pregnancy (wk)	40.27 ± 1.33	38.90 ± 2.04	<0.001
Apgar test (at 5 min)	8.78 ± 1.11	8.60 ± 1.47	n.s.
Apgar test (at 10 min)	9.70 ± 0.70	9.66 ± 1.42	n.s.
Age of father (yr)	33.28 ± 5.41	32.20 ± 4.72	n.s.
Age of mother (yr)	30.59 ± 5.31	30.74 ± 4.79	n.s.
Prematurity (%)	0	6.5	n.s.
Lactation (%)	90	90.9	n.s.
Time of lactation (months)[a]	3.27 ± 3.22	2.76 ± 2.31	n.s.
Education level of mother (%)[b]	14.8	17.5	n.s.
Education level of father (%)[b]	10.0	15	n.s.
Siblings (yes) (%)	52.5	44.8	n.s.

Prematurity indicates ≤36 wk pregnancy. [a] Adjusted for the age of the children at the time of the study.[b] Education level indicates Percentage with university studies *vs.* other categories: 1) basic knowledge of reading and writing; 2) primary studies; 3) secondary studies; M, Males; F, females; n.s., not significant.

Iodine intake and urinary iodine

The urinary iodine in the 31 women who had miscarriages between 8–13 wk gestation who presented to the Gynecology Service of the Osuna Hospital at the start of the study was 69.08 ± 73.25 μg/liter. The control group had significantly lower urinary iodine levels than the 300 group in the third trimester and similar levels to the women from Osuna who had miscarriages (Table 2).

The iodine in the urine of the newborns and in the milk of the mothers was significantly higher in the mothers in the 300 group than those in the control group ($P < 0.0001$) (Table 2). The mothers who did not have their milk iodine measured and the mothers of the children whose urinary iodine was not measured were of a similar age and cultural level as the mothers who did have these measurements (data not shown).

Just 30% of the women reported using iodized salt. At no point in the study did the urinary iodine differ significantly according to the intake of iodized salt (data not shown).

Thyroid function

The plasma levels of thyroid hormones in the control group were only measured in the third trimester. The TSH, FT4, and FT3 levels were significantly higher in the control group (Table 2).

The levels of FT4 ($P = 0.0001$) and FT3 ($P = 0.002$) fell significantly during pregnancy (Table 2). The reduction in FT4 during the second and third trimesters compared with that seen in the first trimester correlated significantly with urinary iodine levels (urinary iodine in the first trimester, $r = 0.29$; $P = 0.05$; urinary iodine in the second trimester, $r = 0.48$; $P = 0.01$; and urinary iodine in the third trimester, $r = 0.35$; $P = 0.01$). The women who had the highest urinary iodine levels experienced the lowest reduction in FT4 during pregnancy.

In the women whose thyroid function was evaluated at two points during the first trimester, the FT4 and the FT3 were significantly lower ($P < 0.0001$) during the second part of the first trimester, with no significant differences in TSH or thyroglobulin (Table 2).

The FT4 in the first trimester correlated significantly with the FT4 in the second ($r = 0.58$; $P < 0.0001$) and the third trimesters ($r = 0.61$; $P < 0.0001$). The neonatal (umbilical cord) TSH was significantly higher in the children of the mothers who had taken 300 μg than the control group ($P < 0.0001$) (Table 2).

Neurodevelopmental evaluation

The MDI did not differ significantly according to the group. The PDI, however, was significantly greater in the children whose mothers had received 300 μg of iodine

TABLE 2. Urinary iodine concentration, TSH, FT3, FT4, and thyroglobulin in the three trimesters of pregnancy and the iodine concentration in maternal milk

	Control group	300 group	*P* value
Urinary iodine			
First trimester (<10 wk)		153.48 ± 110.39	
First trimester (>10 wk)		213.45 ± 127.86	
Second trimester		252.39 ± 121.41c	
Third trimester	87.61 ± 62.06	263.04 ± 120.75	<0.001
Baby[a]	114.55 ± 60.86	203.53 ± 150.60	0.002
Iodine maternal milk[b]	103.88 ± 58.81	181.37 ± 119.45	0.005
TSH			
First trimester (<10 wk)		1.85 ± 1.51	
First trimester (>10 wk)		1.95 ± 1.20	
Second trimester		2.07 ± 1.02	
Third trimester	2.47 ± 1.01	1.99 ± 0.96	0.01
Umbilical cord of infant	3.77 ± 2.81	7.93 ± 5.06	<0.001
FT4			
First trimester (<10 wk)		10.55 ± 1.68	
First trimester (>10 wk)		8.84 ± 1.19	
Second trimester		7.92 ± 1.18	
Third trimester	8.98 ± 1.13	7.77 ± 1.39	<0.001
FT3			
First trimester (<10 wk)		3.06 ± 0.41	
First trimester (>10 wk)		2.89 ± 0.39	
Second trimester		2.72 ± 0.45	
Third trimester	2.96 ± 0.28	2.72 ± 0.43	0.001
Thyroglobulin			
First trimester (<10 wk)		21.19 ± 14.57	
First trimester (>10 wk)		25.70 ± 44.34	
Second trimester		17.10 ± 11.65	
Third trimester		15.38 ± 11.34	

The inclusion of mother's or father's education level in the model did not contribute significantly to the explanation of the variance in PDI.

[a] n = 105 (control group = 30; 300 group = 75).

[b] n = 88 (control group = 21; 300 group = 67).

($P = 0.02$) (Table 3). Most (90%) of the mothers breast fed their infants, for a mean of 3.57 ± 2.88 months. An ANOVA model showed that lactation was a confounding variable in the explanation of the variance in the PDI. In fact, the highest PDI values in the 300 group were only seen in the children who had been breast fed ($P < 0.0001$) but not in those who had not (n = 19) (data not shown). The PDI in the children of the 300 group (but not the control) correlated significantly with the FT4 levels during the third trimester (r = 0.50; $P < 0.0001$) (Fig. 1). The children of the mothers who experienced a lower fall in FT4 during pregnancy were those who also had the highest PDI (r = −0.54; $P < 0.001$) (Fig. 2).

The PDI correlated significantly with the umbilical cord TSH (r = 0.17; $P = 0.019$). An ANOVA model, however, showed that the variation in PDI was only explained by the group ($P = 0.04$), not by the umbilical cord TSH ($P = 0.48$).

In the Bayley Scales of Infant Development, the results of the BRS are expressed according to the mode of each group. Table 4 therefore presents the likelihood that any of the items on the BRS is the same or higher than the mode for each age group. A behavior more in agreement with their age group was seen in the 300 group as compared with the control group for the following items: reaction to

TABLE 3. MDI, PDI, and difference between the two

	Control group	300 group	*P* value
MDI	108.90 ± 13.41	109.22 ± 11.73	n.s.
PDI	102.65 ± 14.60	108.74 ± 13.74	0.02
MDI − PDI	9.65 ± 8.76	9.47 ± 7.70	n.s.

n.s., Not significant.

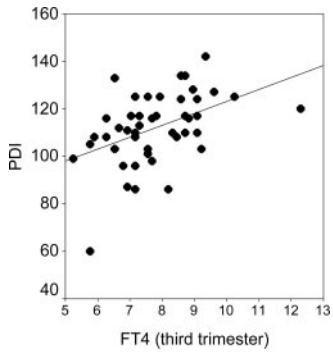

FIG. 1. Correlation between FT4 in the third trimester (300 group) and the PDI (r = 0.50; $P < 0.0001$).

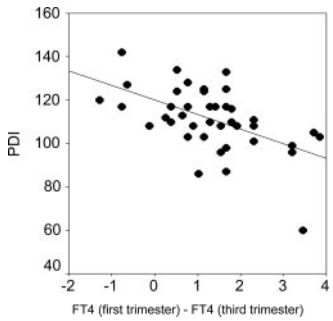

FIG. 2. Correlation between the reduction in FT4 during pregnancy and the PDI in the children. Difference between the third and first trimester *vs.* PDI ($r = -0.54$; $P < 0.001$).

persons ($P = 0.02$), reaction to the mother ($P = 0.05$), cooperation ($P = 0.008$), activity ($P = 0.01$), arousal ($P = 0.04$), and producing sounds by banging ($P = 0.001$).

None of these variables was significantly different according to sex of children.

Discussion

The most relevant results of this study were that children whose mothers received 300 μg of iodine daily from the first trimester had a more favorable psychomotor evaluation than those of mothers who were not treated, independently of the education level of the family.

The World Health Organization recommends 250 μg of iodine supplements in the diet of pregnant women in areas where not everybody consumes iodized salt (14). Because of the reduction in iodine intake in the United States (15), the American Thyroid Association has recommended that U.S. women receive a supplement of 150 μg of iodine daily during pregnancy and lactation and that vitamins for prenatal use or use during pregnancy should be enriched with 150 μg of iodine (16). However, only 15–30% of European women habitually receive iodine supplements (14), and the consumption of iodized salt in Spain varies greatly between the different regions (17).

As expected (14), urinary iodine excretion was significantly greater in the 300 group, as was the iodine content of the milk and the urine of the newborns of the mothers who had received iodine supplements. The FT4 fell over the three trimesters, as seen in most other studies (7, 18). The drop in thyroid hormones is known to occur especially in situations of insufficient iodine supply (6).

Paradoxically, the control group in our study had higher FT4 levels in the third trimester, and the neonatal TSH values were higher in the group whose mothers had

TABLE 4. Likelihood (OR) and 95% confidence interval (CI) that the BRS is above the mode for the age group of each child

	Independent variable (BRS)			
	300 group		Control group (RC)	
Dependent variable	OR (95% CI)	P_{crude}	OR (95% CI)[a]	$P_{adjusted}$[a]
Reaction to persons	6.78 (1.65–27.77)	0.08	6.93 (1.27–37.74)	0.02
Reaction to examiner	0.79 (0.29–2.17)	0.65	0.71 (0.23–2.12)	0.54
Reaction to mother	4.28 (1.69–10.86)	0.02	2.68 (0.95–7.50)	0.05
Cooperation	17.29 (2.00–148.86)	0.009	22.45 (2.22–226.88)	0.008
Fear	1.69 (0.60–4.74)	0.31	0.96 (0.30–3.10)	0.95
Stress	2.32 (0.87–6.13)	0.08	2.19 (0.75–6.31)	0.14
Emotional tone	0.98 (0.29–3.35)	0.98	1.27 (0.33–4.84)	0.72
Reaction to objects	0.29 (0.03–2.41)	0.25	0.57 (0.05–5.55)	0.63
Creative play with materials	1.76 (0.58–5.33)	0.31	1.29 (0.38–4.32)	0.67
Intentionality	0.98 (0.18–5.32)	0.99	1.61 (0.24–10.65)	0.62
Attention	8.55 (1.64–44.44)	0.01	3.93 (0.67–23.03)	0.12
Perseverance	0.69 (0.30–1.55)	0.37	0.80 (0.33–1.91)	0.62
Activity	8.55 (1.64–44.44)	0.01	9.67 (1.61–58.11)	0.01
Arousal	2.68 (0.73–9.84)	0.13	5.87 (1.03–33.40)	0.04
Looking	0.33 (0.04–2.83)	0.31	0.21 (0.02–2.10)	0.18
Producing vocal sounds	1.52 (0.70–3.30)	0.28	1.23 (0.53–2.86)	0.62
Producing sounds by banging	9.00 (2.66–30.44)	0.00	10.24 (2.51–41.72)	0.001
Handling	2.50 (0.88–7.03)	0.08	2.19 (0.68–7.04)	0.18
Moving the body	0.81 (0.34–1.93)	0.64	0.59 (0.23–1.54)	0.28
Biting or sucking				
Fingers	1.07 (0.38–3.01)	0.89	0.71 (0.23–2.24)	0.56
Pacifier	0.82 (0.08–8.13)	0.86	0.65 (0.05–7.76)	0.73
Toys	2.00 (0.89–4.49)	0.09	1.59 (0.66–3.85)	0.29

BRS: 1 = below the mode for the age group; 2 = the same or above the mode for the age group. RC, Reference category.

[a] Because the week of gestation was significantly associated with the test results, the strength of the association between the BRS and the control group *vs.* 300 group was also adjusted for the week of gestation and prematurity.

received 300 μg of iodine. These results are, to a certain extent, unexpected. The higher FT4 levels in the third trimester in the control group could be because, as the group was not selected, the thyroid hormones were measured nearer to the date of delivery than in the other group. A hemoconcentration secondary to a loss of intravascular volume occurs at the end of gestation (19), which would also explain the higher FT3 values although the T_3/T_4 ratio was unchanged.

Changes in the cord blood TSH concentration, from a median of 7.07 to 9.00 mIU/liter in infants born to women with mild to moderate iodine deficiency who had received a daily supplement of 150 μg as compared with infants from nonsupplemented mothers have been interpreted as evidence of undesirable and potentially harmful effects of maternal iodine supplementation for the child (20). However, recent studies have shown that, unexpectedly, the levels of TSH and FT4 in cord blood correlate positively (21, 22). The increase found in the cord serum TSH concentration was actually the expected change, considering that there was a positive correlation between the fetal TSH concentration and FT4. It should not be interpreted as indicating a potentially harmful effect of iodine supplements on the mother (22).

This study was undertaken in a population in which only 30% consume iodized salt and with a mean urinary iodine concentration in pregnant women less than 100 μg/liter (7). Previous studies in these populations have shown the existence of iodine deficiency disorders, represented by a negative association between iodine intake, the hearing threshold (23), and the IQ of school-age children (2).

Experimental studies in newborn animals of mothers with low T_4 levels during pregnancy have found that low T_4 levels during pregnancy trigger irreversible damage in the cytoarchitecture of the fetal brain (24–27). Other clinical and epidemiological studies have examined the role of T_4 levels during pregnancy in relation to the neurodevelopment of children. Although these studies are numerous, many lack a control group and differ in their design, the procedures used for psychometric evaluation, and the time of evaluation of the children. Most of these studies found neurodevelopmental disorders in the children of mothers who had low T_4 levels during pregnancy (28–32), although not all the studies found this association (33, 34).

To evaluate neuropsychological development in our study, we used the Bayley Scales of Infant Development, which comprise three scales designed to study children aged 0 to 2.5 yr of age and have also been used in other studies (1, 10, 32, 34). The children of mothers who took 300 μg of iodine scored better on the PDI, and many of the items related to the BRS were significantly more favorable in these children as compared with the control group. These results were expected but were apparently contradictory to the results for cord TSH levels in the same group. Some studies suggest that fetal TSH may act as a growth factor for the brain (35, 36). In this case, the increase found in this study could even be considered a beneficial consequence of iodine supplements during infancy (22). It does not seem to have had consequences on the neurodevelopment of the children studied. In fact, in the children of the mothers who had 300 μg, a good correlation was found between neurodevelopment and FT4 levels during the third trimester, which may indicate the beneficial effects of raising FT4 levels at any time during pregnancy. Of special interest was the observation that the children of the mothers who experienced a lower reduction in FT4 also had higher values on the PDI, suggesting that avoiding a reduction in FT4 during pregnancy is just as important as maintaining adequate levels during the first trimester.

The children of mothers who consumed 300 μg of potassium iodine during pregnancy had a more satisfactory supply of iodine after birth via the maternal milk, as shown by the higher iodine concentration in the milk. Moreover, an ANOVA model showed a clear interaction between iodine dose and lactation in neurodevelopment; this effect of the 300 μg dose on neurodevelopment was only found in the children who had received maternal milk. Various studies have shown that iodine enrichment after delivery and adequate T_4 levels during infancy are associated with a greater intellectual capacity of children (2, 34, 37–39).

This study has certain strengths, because it was an interventional study and not just observational, and a few limitations, such as the need to adjust for confounding variables and the fact that the control group was only included from the third trimester of pregnancy, and finally that it was not a randomized controlled trial. Although the intake of iodine was started in the first trimester, it is possible that iodine prophylaxis begun even earlier during pregnancy might have other effects, such as modifying the FT4 levels in the first trimester, or similar effects with different doses (40).

The number of premature children was similar in both groups. Nevertheless, it is important to point out that premature, low birthweight and very low birthweight infants are more sensitive to iodine, and an elevated TSH in these neonates may have a different implication on neurodevelopmental outcome. The effects of a supplement of 300 μg of potassium iodine in pregnant women on the neurodevelopmental outcome in premature or low birthweight offspring is likely to be different from that in full-term children.

In summary, the results of this study suggest that in a population with a moderate iodine deficiency in the diet, the prescription of iodine supplements, at least in the dose

used here, is able to reduce the usual fall in FT4 during pregnancy. Additionally, dietary iodine supplements at the dose used here not only have no harmful effects on the neurodevelopment of the children, as might be deduced from their effect on the TSH levels of the newborns, but also may be beneficial, probably in relation to the greater supply of iodine during maternal lactation in those mothers who continue potassium iodine supplements after giving birth. Thus, further research seems called for to study the best form, amount, and time for iodine prophylaxis during pregnancy. Notwithstanding these suggestions, possible confounding variables not controlled for in this study mean that the results should be considered preliminary.

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