TITLE

Impact of dietary habit, iodine supplementation and smoking habit on urinary iodine concentration during pregnancy in a Catalonia population.

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ABSTRACT

Background: The nutritional status of women during pregnancy can have a considerable effect on maternal and fetal health, and on perinatal outcome. **Aim:** to assess the changes occurring in dietary iodine intake, KI supplementation, and smoking habit, and the impact of these changes on the urinary iodine concentration (UIC) during pregnancy in a population of women in Catalonia (Spain). **Methods:** Between 2009-2011 an observational study including a cohort of women whose pregnancy was monitored in the publically-funded health system in a central region of Catalonia. Women received individual educational counseling imparted, a dietary questionnaire was completed, and a urine sample collected for iodine determination at each trimester visit. **Results:** 633 (67.9%) women answered the questionnaire at all 3 visits. The percentage of women with a desirable UIC (≥150µg/L) increased from the first to the second trimester and remained stable in the third (57.3%,68.9%,68%; p<0.001). Analysis of the relationship between UIC≥150 µg/L and the women's dietary habits showed that the percentage with UIC≥150 µg/L increased with greater consumption of milk, fresh vegetables, and fruit in the first trimester, and the same was true for iodized salt use in all three trimesters and iodine supplementation in all three. **Conclusion:** During pregnancy increased intake of milk, iodized salt, and iodine supplements was associated with an increase in the UIC.

Trial Registration **ClinicalTrials.gov: NCT01301768**

KEYWORDS

Pregnancy; Iodine; Dietary habits; Iodine supplement, Urinary iodine concentration

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INTRODUCTION

Iodine is an essential nutrient required for synthesizing thyroid hormones, which regulate the body's metabolism, growth, and development. Iodine requirements increase significantly during pregnancy and lactation, and if the intake is insufficient during these periods, thyroid hormone production can decrease, with consequent repercussions on the mother, the developing fetus, and the breastfed infant[1]. Severe or moderate iodine deficiency during pregnancy and lactation can affect the mother's and newborn's thyroid function, as well as the child's later neuropsychological development [1]. According to the 2014 position statement of Spanish Society of Endocrinology and Nutrition [2], several studies have shown that most Spanish mothers are iodine-deficient during pregnancy and lactation. Nonetheless, two recent studies performed in pregnant women in the first trimester, one in Asturias [3] and the other by our group in Catalonia [4], reported median urinary iodine levels of 197 μg/L and 172 μg/L, respectively, both values within the margins the World Health Organization (WHO) considers indicative of adequate iodine nutrition (>150 μg/L). The foods that had the greatest impact on urinary iodine in these studies were iodized salt, milk, and also iodine supplements.

Appropriate nutritional habits together with iodine supplementation can help meet iodine requirements during pregnancy and postpartum, and prevent or correct iodine deficiency and its consequences [5]. Most foods contain relatively little iodine, and to ensure that intake of this element is sufficient in each individual, the WHO and the United Nations International Children's Emergency Fund (UNICEF) recommend universal salt iodization as a global strategy [6]. When iodized salt intake is of a voluntary nature, populations at higher risk, such as pregnant women, breastfeeding mothers, and children under two years of age, may not receive a sufficient amount of iodine unless periodic campaigns are conducted to encourage iodized salt consumption.

Health education regarding nutrition during pregnancy aims to improve the quality of the diet, instructing women on which foods and what amounts of food should be consumed to achieve an optimal dietary intake. It should also include advice on the use of various micronutrient supplements containing iron, folic acid, and iodine [7]. About iodine, women who are planning pregnancy and those who

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are pregnant, or breastfeeding should be encouraged to consume iodized salt, milk, and dairy products to obtain an adequate iodine supply. Potassium iodide (KI) supplements (150-200 µg/day) also guarantee adequate intake of this element [2]. Another important aspect of health education during pregnancy is the recommendation to stop smoking. Among other harmful effects, tobacco is considered a goitrogenic substance that interferes with iodine uptake by the thyroid glands [8,9].

In Catalonia, the nutritional recommendations provided during pregnancy are aimed at maintaining a healthy weight, suppressing the use of tobacco and alcoholic beverages, and establishing a balanced, healthy diet. A healthy diet should be sufficient, complete, varied, and balanced, but also adapted to the characteristics of the individual, satisfying, safe, sustainable, and affordable. To cover iodine needs during pregnancy, the diet should contain 3 servings of milk and dairy products and 2 g of iodized salt per day. If this iodine supply cannot be guaranteed, IK supplementation (200-250 µg/day) is recommended (Generalitat de Catalunya, Departament de Salut, 2018).

Few studies in our setting have focused on the changes in iodine nutrition that occur during pregnancy and the possible relationship between iodine status and dietary habits. Hence, this study aimed to investigate the effects of dietary iodine intake, KI supplementation, and smoking habit on iodine status in a population of pregnant women in Catalonia.

1. METHODS

Design

Observational study carried out in a cohort of pregnant women monitored in the publically-funded health care system of the central area of Catalonia (Spain). Initially, the study was contemplated as part of a clinical trial project to evaluate the efficacy of an educational intervention imparted in groups to promote iodine intake and optimal urinary iodine concentrations (≥150 µg/L) in pregnant women. The women were enrolled, but the intervention by groups was found to be impracticable in our setting because of difficulties to ensure proper development of the educational program. Hence, the design was converted to an observational study with a single-arm (usual clinical practice) cohort in which women received the educational counseling on an individual basis. As a part of

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the routine clinical practice in our primary care centers, midwives impart information on diet and other relevant recommendations at a prenatal visit during the first trimester of pregnancy.

The study was conducted within the framework of the primary care center Program for Sexual and Reproductive Health Care (PASSIR) of the Catalonian central and northern metropolitan regional offices of the *Institut Català de la Salut* (ICS, Catalan Institute of Health) in the province of Barcelona.

Participants

Consecutive recruitment was carried out during 2008 and 2009. All women older than 17 years attending the participating centers in their first trimester of pregnancy (<13 weeks) and accepting to participate were included in the study. Pregnant women with thyroid disease, no telephone contact, or difficulty communicating with the health personnel (cognitive, sensory, or language problems), and those refusing to participate, were excluded.

Data collection

Each trimester, a visit was scheduled in the participating primary care centers where women answered a questionnaire and a urine sample was collected for iodine determination. The questionnaire compiled socio-demographic data, including patient age, place of origin, place of residence (rural/urban), and educational level. Information on dietary habits and other factors was collected at a personal interview by primary care midwives, using a standardized questionnaire [11] that showed good reliability (Cronbach's alpha, 0.960 and intraclass correlation coefficient, 0.927). The questionnaire contained items related to consumption of cow milk (glasses/day; 1 glass = 200 mL), yogurt (units/week), cheese (portions/week), cooked vegetables, fresh vegetables, fish, canned fish, meat, cold cooked meats, eggs, fruit, and dried fruit (servings/week), regular consumption of iodized salt and daily use of iodine supplements (KI or iodine vitamin supplements) (Yes/No), and tobacco use.

Urinary iodine concentration (UIC) was determined as follows: A first-morning urine sample was collected from each woman, quickly frozen at −40°C, and transported within 24 to 48 h to a central laboratory (Barcelona Hospital Clinic), where UIC determination (μg/L) was performed using the Benotti and Benotti method [12,13]. Urine was digested with chloric acid and then underwent the Sandell-Kolthoff reaction, in which iodine was determined by its action as a

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catalyst in the reduction of ceric ammonium sulfate in the presence of arsenious acid. The inter-assay and intra-assay coefficients of variation of the technique were 15.5% and 12.6%, respectively. Three times a year, the UIC assay undergoes evaluation by an external quality assessment program from the Spanish Association of Neonatal Screening (AECNE). UIC values obtained were dichotomized as <150 µg/L (insufficient) and ≥150 µg/L (adequate) [14].

Statistical analysis

Quantitative variables are described as the mean and standard deviation or the median and first-third quartiles (Q1-Q3) for those with a non-normal distribution. Categorical variables are expressed as the absolute frequency and percentage. The Student *t* test for independent data and the Mann-Whitney *U* test, as appropriate, were used to compare the quantitative variables, and the Pearson chi-square test for categorical variables.

The intake information was grouped into 3 categories (milk: 0, 1-2, >2 glasses; yoghourt: 0, 1-2, >2 units; cheese: 0, 1-2, >2 portions; and the remaining: 0, 1-2, >2 servings). Multilevel mixed-effects logistic regression models adjusted for paired measures in the 3 trimesters were performed to assess the effect of iodine-rich food intake or supplementation on UIC values ≥150 µg/L.

The initial regression model included all variables that were individually associated with the outcome at a significance level of p<0.10. The final model included variables that were statistically significant at p≤0.05; the Akaike information criterion and biological plausibility were also taken into consideration. Missing values for food intake at follow-up were imputed using all available variables. The estimation model was based on 10 replicates and included the same variables as in the final hierarchical model.

Statistical significance was set at p≤0.05 (two-tailed). Data were analyzed with SPSS version 23.0. Multiple imputation and mixed-effects logistic regression analyses were performed with the Stata/SE Statistical Package 14.0 for Windows.

2. RESULTS

In total, 970 women who attended a first-trimester prenatal visit were included. Among them, 945 (97.4%) answered the dietary questionnaire at this visit, 752 (77.5%) attended the second-trimester visit, and 705 (72.7%) the third-trimester

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visit (Table 1). The 633 (67.9%) women who answered the questionnaire at all 3 visits showed no significant socio-demographic differences relative to those who did not.

In the first trimester evaluation, mean age was 30.6 (4.6) years, 83% of participants were Spanish natives, and 73.7% lived in an urban setting. As to educational level, 3.5% were illiterate or had not completed primary school, 24.6% had a primary school diploma, 41.6% a high school diploma, and 30.4% a university degree.

The results of the dietary questionnaire are summarized in Table 1. The column corresponding to the first trimester shows the dietary habits women had when they went to the first prenatal visit. At that time, they each received counseling on nutritional health according to the usual clinical practice. The columns for the second and third trimesters show the dietary habits acquired following educational counseling.

In general, consumption of milk, cooked and fresh vegetables, fish, meat, eggs, and fruit increased along the three trimesters ($p<0.05$) (Table 1). Yoghourt intake increased, but only to a marginally significant degree ($p=0.070$). Consumption of cheese, cold cooked meats, and dried fruit showed no changes. Iodized salt use increased considerably in the second trimester and held steady in the third (35.7%, 85.4%, 88.9%; $p<0.001$). The same trends were seen for iodine supplementation (46.8%, 88.8%, 87.6%; $p<0.001$). Tobacco use decreased somewhat in the second trimester and was maintained in the third, with only marginal significance (24.1%, 20.0%, 19.5%; $p=0.056$). The median UIC increased from the first to the second trimester and held steady in the third (172 µg/L, 210 µg/L, and 202.5 µg/L, respectively; $p<0.001$).

Association with UIC ≥150 µg/L

Urinary iodine values were dichotomized into <150 µg/L and ≥150 µg/L. The percentage of women with a desirable UIC level (≥150 µg/L) increased from the first to the second trimester and held steady in the third (57.3%, 68.9%, 68%; $p<0.001$) (Table 1)

Analysis of the relationship between UIC ≥150 µg/L and the women's dietary habits (Table 2), showed that the UIC increased as consumption of milk, fresh vegetables, and fruit increased in the first trimester, and the same was true

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for iodized salt consumption in all three trimesters and iodine supplementation in all three trimesters. Tobacco consumption did not related with the iodine status

Multivariate analysis

We carried out a multilevel mixed-effects logistic regression analysis of repeated measures to determine which intake-related factors were associated with UIC <150 µg/L. Variables that were candidates for inclusion in the analysis were examined (Table 3). The resulting multivariate model (multilevel mixed-effects) is shown in Table 5A. A protective effect was manifested for iodine supplementation (OR=0.42, 95% CI [0.34-0.52]; p<0.001), iodized salt intake (OR=0.67, 95%CI [0.54-0.83]; p<0.001), and milk consumption (1-2 glasses: OR=0.68, 95%CI [0.52-0.90]; p=0.006; >2 glasses: OR= 0.64, 95%CI [0.45-0.90]; p=0.011).

After carrying out multiple imputation of missing values in any of the three trimesters (Table 4) and repeating the process of variable selection, we obtained the same model as the previous one (Table 5B: multilevel with imputation), in which the protective role of each of the factors was maintained. The model with imputation provided OR values and confidence intervals very similar to those in the model without imputation.

Table 1. Characteristics and habits of the participants, based on their responses to the dietary questionnaires

Table 2. Percentage of pregnant women with UIC ≥150 µg/dL related to dietary intake, iodized salt intake, iodine supplementation, and smoking

Table 3. Individual effect of each variable included in multilevel mixed-effects logistic regression models adjusted for paired measures in the 3 trimesters to assess the effect of iodine-rich food intake or supplementation on UIC values ≥150 µg/L

Table 4. Summary of the missing data imputation

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Table 5. Results of multilevel mixed-effects logistic regression models adjusted for paired measures in the 3 trimesters to assess the effect of iodine-rich food intake or supplementation on UIC values ≥150 μg/L

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3. DISCUSSION

The results of this study showed favorable changes in iodine nutrition in a sample of pregnant women from central Catalonia following individual educational counseling on dietary habits imparted by the midwife in the first trimester of pregnancy. The median UIC increased from the first to the second trimester and held steady thereafter (172, 210, and 202.5 µg/L, respectively). These changes were related to greater consumption of milk, iodized salt, and iodine supplements. The data indicate that iodine nutrition is adequate in pregnant women in our setting, in accordance with the recommendations of the WHO, the International Council for the Control of Iodine Deficiency Disorders (ICCIDD), and the United Nations International Children's Emergency Fund (UNICEF), which recommend a population median of >150 µg/L [6].

The daily iodine intake recommended by the WHO during pregnancy and lactation is at least 250 µg/day. However, it is difficult to estimate iodine intake through analysis of the diet, as the amount of this micronutrient in both food and water can vary considerably from one area to another. In normal conditions there is a balance between iodine intake and urinary iodine elimination, which makes determination of the UIC in casual urine specimens a reliable indicator of the iodine nutritional status of populations [15]. Evidently, a median UIC increase also implies a significant gain in the percentage of individuals with UIC values ≥150 µg/L. However, because of the considerable variability in urinary iodine level, this cut-off is not considered acceptable to differentiate between populations with adequate or poor iodine nutrition. Only the median UIC is deemed indicative of the iodine nutrition status in a specific population, such as pregnant women [16]. Nonetheless, some studies have shown that pregnant women with UIC <150 µg/L can have a higher risk of goiter [17]. Prematurity and low birth weight are more prevalent in their newborns [18,19], their children may show a lower IQ (median <150 µg/g creatinine) [20,21] and greater oxidative stress [22]. Hence, it is likely that women with urinary iodine below this cut-off have a higher risk of iodine deficiency and greater morbidity, which can also extend to their offspring [23]. In the present study, the median UIC was adequate,

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but a substantial percentage of women (44.7% in the first trimester and 32% in the third) had levels <150 µg/L and, likely, a greater risk of morbidity.

The probability of developing iodine deficiency-related disorders is undoubtedly higher when the median UIC does not reach 150 µg/L. However, a large part of the studies conducted in Europe over the last few years have reported median UIC values considerably lower than this limit, and even below 100 µg/L [24–32]. Only a few countries such as Iceland [33] and Holland [34] have reported median values in pregnant women higher than 150 µg/L. Thus, many of the studies conducted provide evidence that most pregnant women in Europe have insufficient iodine intake even in areas with adequate iodine nutrition [35]. Our results coexist with findings of excellent iodine nutrition in children in our setting [36] and adequate nutrition in the general population [37,38], despite the borderline situation in women of childbearing age.

The UIC changes observed over pregnancy have been a subject of debate, particularly in iodine-deficient areas. Some studies, such as one conducted in the United Kingdom [24], have shown a significant increase in the median UIC (from 42 µg/L in the first trimester to 69.4 µg/L in the third, or a creatinine increase from 103 µg/g to 126 µg/g). These changes were associated with an increase in consumption of dairy products as pregnancy progressed. Similar findings have been reported in studies from Norway (from 66 µg/L to 92 µg/L) [25] and Ghana [39], and in other studies carried out in Spain (Basque Country [40], Jaén [41] and Osuna[42]). In the three Spanish studies, the increase was clearly related to KI supplementation, received by most of the women included. Of note, in the study performed in Jaén, women who consumed iodized salt during the year before they became pregnant maintained a median UIC >150 µg/L over the entire pregnancy. In contrast, other studies, such as those by Stilwell [43], Brander [44], and Koukkou [45], have reported UIC decreases with progression of pregnancy. This would be explained mainly by depletion of iodine deposits due to increased requirements without adequate dietary compensation. In addition, the drop in UIC could be enhanced by pregnancy-related physiological changes in the glomerular filtration rate. Other studies, however, have reported no significant changes in the UIC over the three trimesters. [26,46].

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In the present study, the dietary habits that had an impact on the IUC were consumption of milk and iodized salt, as well as KI supplementation. These findings concur with the results obtained in the study by Bath [24] in the United Kingdom, where daily milk intake (>280 mL) and consumption of Brazil nuts had an impact on the UIC. Among the pregnant women studied, 97% did not receive iodine supplements and only 6% used iodized salt. Similar findings were reported in the study by Dhal [25] in Norway, which showed that the dietary habits with the greatest effect on the UIC were consumption of dairy products and iodine supplementation (15.1% of pregnant women). There was no information on iodized salt consumption in that study. The authors found that intake of milk and dairy products had a greater impact on the IUC than seawater fish and other marine products. In the study by Henjum [26], the factor with the greatest impact on the IUC during pregnancy was iodine supplementation, whereas in the study by Shashi Kant [47] in India, it was iodized salt intake (90.9% of pregnant women), although the median amount of iodized salt consumed was high, at 8.3 g/day.

Dairy products are an important source of iodine in numerous European countries, as evidenced in the study by Bath in the United Kingdom [24], Dahl in Norway [48], and some studies performed in Spain. Two Spanish studies have reported that milk is an important source of dietary iodine [49,50]. In our country, a glass of ordinary milk (200-250 mL) provides an average of 50 µg of iodine or 20% of the recommended amount for pregnant women and breastfeeding mothers. The study by Menéndez [3] also showed an increase in the UIC with intake of 2 or more daily servings of milk or milk products.

In the present study, vegetable consumption did not remain in the final model as having a significant impact on the IUC, in accordance with the 2007-2012 study by NHANES showing no correlation between vegetable intake and the UIC [51]. Fortification of certain vegetables with iodine has been successfully undertaken to increase iodine intake [52], but this option is not contemplated in our setting.

Nutritional education and counseling during pregnancy is focused on improving the quality of the diet. Women are provided information on what foods and what amounts of food are needed to achieve proper nutrition, and they are

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instructed on the use of micronutrient supplements such as iodine when adequate amounts are not guaranteed by the diet [7]. We found an increase in consumption of iodine-rich foods from the first to the second trimester that was maintained in the third following dietary health counseling performed by the midwife on an individual basis during the first trimester. These findings concur with those of O'Kane [53], who reported that women who received information on the importance of iodine during pregnancy increased their intake of this micronutrient. In contrast, Amiri [54] reported that knowledge of the importance of iodine and iodized salt intake was enhanced after an educational intervention in pregnant women, but there was no parallel improvement in their iodine status. Nonetheless, the authors advocated improving health literacy in pregnant women as an essential strategy.

4. LIIMITATIONS:

This research was the impossibility to carry out the group of nutrition education intervention as planned in order to promote iodine consumption during pregnancy. As it has been mentioned, an individual nutrition education intervention was carried out in the midwife's prenatal control surgery. However, the longitudinal design of the study allows us to attribute to it the changes observed in the iodine intake in the 2nd and 3rd trimester and its effects on the iodine status.

As for future research, the results of this study could be extended with a further research which would have the objective of establishing the impact of eating habits and iodine supplements on UIC amongst breastfeeding mothers during postpartum.

5. CONCLUSION

In conclusion, the individual educational counseling on proper diet and nutrition carried out by the midwife during the routine first trimester prenatal visit had a positive impact on consumption of iodine-rich foods in pregnant women. Greater intake of milk and iodized salt, as well as KI supplementation was associated with an increase in the UIC. As a result, the median UIC in the pregnant population in central Catalonia rose from the first to the second trimester of pregnancy and was sustained in the third. These data indicate adequate iodine nutrition in the pregnant population of this area, in accordance with the WHO, ICCIDD, and UNICEF recommendations.

Thus, a dietary educational intervention should be considered an essential component of pregnancy management to promote optimal iodine nutrition. The benefits obtained will contribute to decreasing fetal and maternal morbidity, as well as morbidity in the breast-fed infant. In addition, the knowledge gained can lead to better dietary habits in women beyond pregnancy.

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Availability of data and materials

The data supporting the conclusions of this study are available upon reasonable request and under the supervision of IDIAP Jordi Gol.

Authors' contributions

MTT have made substantial contributions to the conception and design, acquisition of data, analysis and interpretation of data. GP, PT and GF have made substantial contributions to the conception and design. RC carried out laboratory determinations of the project. LF, LLV and JMM have made substantial contributions to the conception and design, and interpretation of data. All authors read and approved the final manuscript.

Authors' information

Not applicable.

Ethics approval and consent to participate

All women were informed and signed their informed consent to participate in the project.

The study was approved by the Clinical Research Ethics Committee at the Primary Care Research Institute (IDIAP) Jordi Gol (Code: **P07/02)**.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflicts of interest

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Table 1. Characteristics and habits of the participants based on their responses to the dietary questionnaires

	T1 (n=945)	T2 (n=752)	T3 (n=705)	p
Age	30.6 (4.6)	30.4 (4.5)	30.4 (4.5)	0.726
Urban setting	363 (73.7%)	551 (73.3%)	523 (74.2%)	0.924
Educational level				
Illiterate	5 (0.5%)	5 (0.7%)	3 (0.4%)	0.999
Primary school education not completed	28 (3.0%)	18 (2.5%)	19 (2.8%)	
Primary school	232 (24.6%)	180 (24.8%)	165 (24.6%)	
High school	393 (41.6%)	297 (40.9%)	274 (40.9%)	
University degree	287 (30.4%)	226 (31.1%)	209 (31.2%)	
Place of origin				
Native of Spain	784 (83.0%)	600 (82.6%)	560 (83.6%)	0.999
South American	71 (7.5%)	53 (7.3%)	46 (6.9%)	
African	52 (5.5%)	43 (5.9%)	39 (5.8%)	
Other	38 (4.0%)	30 (4.1%)	25 (3.7%)	
Milk				
0 glasses	178 (18.8%)	103 (13.7%)	82 (11.6%)	**<0.001**
1-2 glasses	633 (67.0%)	525 (69.8%)	482 (68.4%)	
> 2 glasses	134 (14.2%)	124 (16.5%)	141 (20.0%)	
Yogurt				
0 units	126 (13.3%)	80 (10.6%)	70 (9.9%)	0.070
1-2 units	192 (20.3%)	149 (19.8%)	124 (17.6%)	
> 2 units	627 (66.3%)	523 (69.5%)	511 (72.5%)	
Cheese				
0 portions	131 (13.9%)	77 (10.2%)	80 (11.3%)	0.184
1-2 portions	214 (22.6%)	173 (23.0%)	153 (21.7%)	
> 2 portions	600 (63.5%)	502 (66.8%)	472 (67.0%)	
Cooked vegetables				
0 servings	48 (5.1%)	24 (3.2%)	22 (3.1%)	**0.030**
1-2 servings	289 (30.6%)	212 (28.2%)	185 (26.2%)	
> 2 servings	608 (64.3%)	516 (68.6%)	498 (70.6%)	
Fresh vegetables				
0 servings	51 (5.4%)	25 (3.3%)	21 (3.0%)	**<0.001**
1-2 servings	194 (20.5%)	109 (14.5%)	115 (16.3%)	
> 2 servings	700 (74.1%)	618 (82.2%)	569 (80.7%)	
Fish				
0 servings	58 (6.1%)	29 (3.9%)	25 (3.5%)	**<0.001**
1-2 servings	535 (56.6%)	390 (51.9%)	335 (47.5%)	
> 2 servings	352 (37.2%)	333 (44.3%)	345 (48.9%)	
Canned fish				
0 servings	142 (15.0%)	77 (10.2%)	72 (10.2%)	**<0.001**
1-2 servings	495 (52.4%)	351 (46.7%)	308 (43.7%)	
> 2 servings	308 (32.6%)	324 (43.1%)	325 (46.1%)	
Meat				
0 servings	36 (3.8%)	11 (1.5%)	12 (1.7%)	**0.016**
1-2 servings	123 (13.0%)	97 (12.9%)	89 (12.6%)	
> 2 servings	786 (83.2%)	644 (85.6%)	604 (85.7%)	
Cold cooked meat				
0 servings	133 (14.1%)	127 (16.9%)	115 (16.3%)	0.170

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	1-2 servings	261 (27.6%)	212 (28.2%)	218 (30.9%)	
	> 2 servings	551 (58.3%)	413 (54.9%)	372 (52.8%)	
Eggs					
	0 servings	52 (5.5%)	18 (2.4%)	22 (3.1%)	**<0.001**
	1-2 servings	526 (55.7%)	399 (53.1%)	356 (50.5%)	
	> 2 servings	367 (38.8%)	335 (44.5%)	327 (46.4%)	
Fruit					
	0 servings	38 (4.0%)	17 (2.3%)	11 (1.6%)	**<0.001**
	1-2 servings	89 (9.4%)	46 (6.1%)	35 (5.0%)	
	> 2 servings	818 (86.6%)	689 (91.6%)	659 (93.5%)	
Dried fruit					
	0 servings	366 (38.7%)	286 (38.0%)	284 (40.3%)	0.918
	1-2 servings	351 (37.1%)	285 (37.9%)	260 (36.9%)	
	> 2 servings	228 (24.1%)	181 (24.1%)	161 (22.8%)	
Iodized salt		337 (35.7%)	634 (85.4%)	614 (88.9%)	
Iodine supplementation		446 (46.8%)	656 (88.8%)	605 (87.6%)	
Tobacco consumption					
	Non smoker	633 (65.7%)	555 (67.1%)	557 (67.5%)	
	Ex-smoker	98 (10.2%)	105 (12.8%)	106 (12.8%)	
	Smoker	232 (24.1%)	164 (20.0%)	161 (19.5%)	
UIC, μg/L (*)		172 (104-289)	210 (130–319)	202.5 (131–331)	**<0.001**
UIC ≥150 μg/L		556 (57.3%)	514 (68.5%)	479 (68.0%)	**<0.001**

(*) Median and first-third quartiles (Q1-Q3)

UIC, urinary iodine concentration; T1, T2, and T3, first, second, and third trimester

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Table 2. Percentage of pregnant women with UIC ≥150 µg/dL related to dietary intake, iodized salt intake, iodine supplementation, and smoking

		T1 n=945	p	T2 n=752	p	T3 n=705	p
Milk			**0.016**		0.129		0.543
	0 glasses	85 (47.8%)		63 (61.2%)		51 (63.0%)	
	1-2 glasses	372 (58.8%)		363 (69.4%)		332 (68.9%)	
	> 2 glasses	81 (60.4%)		88 (71.0%)		96 (68.1%)	
Yogurt			0.372		0.468		0.416
	0 units	72 (57.1%)		57 (71.3%)		46 (65.7%)	
	1-2 units	99 (51.6%)		104 (69.8%)		81 (65.3%)	
	> 2 units	367 (58.5%)		353 (67.8%)		352 (69.0%)	
Cheese			0.104		0.689		0.903
	0 portions	69 (52.7%)		51 (66.2%)		53 (66.3%)	
	1-2 portions	115 (53.7%)		118 (68.6%)		108 (70.6%)	
	> 2 portions	354 (59.0%)		345 (68.9%)		318 (67.5%)	
Cooked vegetables			0.561		0.715		0.046
	0 servings	26 (54.2%)		12 (50.0%)		11 (50.0%)	
	1-2 servings	162 (56.1%)		151 (71.6%)		120 (65.2%)	
	> 2 servings	350 (57.6%)		351 (68.2%)		348 (69.9%)	
Fresh vegetables			**0.024**		0.630		0.140
	0 servings	21 (41.2%)		15 (60.0%)		9 (42.9%)	
	1-2 servings	107 (55.2%)		76 (69.7%)		80 (69.6%)	
	> 2 servings	410 (58.6%)		423 (68.7%)		390 (68.7%)	
Fish			0.277		0.927		0.413
	0 servings	31 (53.4%)		15 (53.6%)		16 (64.0%)	
	1-2 servings	299 (55.9%)		275 (70.5%)		235 (70.4%)	
	> 2 servings	208 (59.1%)		224 (67.5%)		228 (66.1%)	
Canned fish			0.184		0.515		0.578
	0 servings	72 (50.7%)		50 (64.9%)		50 (69.4%)	
	1-2 servings	286 (57.8%)		240 (68.6%)		203 (65.9%)	
	> 2 servings	180 (58.4%)		224 (69.3%)		226 (69.8%)	
Meat			0.590		0.147		0.678
	0 servings	18 (50.0%)		6 (54.5%)		8 (66.7%)	
	1-2 servings	71 (57.7%)		77 (79.4%)		63 (70.8%)	
	> 2 servings	449 (57.1%)		431 (67.1%)		408 (67.7%)	
Cold cooked meat			0.529		0.013		0.623
	0 servings	74 (55.6%)		97 (76.4%)		76 (66.7%)	
	1-2 servings	159 (60.9%)		148 (70.5%)		156 (71.6%)	
	> 2 servings	305 (55.4%)		269 (65.1%)		247 (66.4%)	
Eggs			0.383		0.799		0.718
	0 servings	32 (61.5%)		11 (61.1%)		14 (63.6%)	
	1-2 servings	287 (54.6%)		273 (68.8%)		241 (67.9%)	
	> 2 servings	219 (59.7%)		230 (68.7%)		224 (68.5%)	
Fruit			**0.027**		0.862		0.195
	0 servings	17 (44.7%)		12 (70.6%)		9 (81.8%)	
	1-2 servings	44 (49.4%)		30 (65.2%)		26 (74.3%)	
	> 2 servings	477 (58.3%)		472 (68.7%)		444 (67.5%)	
Dried fruit			0.639		0.078		0.653
	0 servings	199 (54.4%)		198 (69.7%)		189 (66.5%)	

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1-2 servings	213 (60.7%)		206 (72.3%)		189 (73.0%)	
> 2 servings	126 (55.3%)		110 (60.8%)		101 (62.7%)	
Iodized salt		**0.001**		**0.030**		**0.004**
No	321 (52.8%)		65 (59.6%)		42 (53.8%)	
Si	217 (64.4%)		449 (70.0%)		437 (69.8%)	
Iodine supplementation		**<0.001**		**0.002**		**<0.001**
No	234 (46.5%)		45 (53.6%)		44 (50.6%)	
Si	304 (68.8%)		469 (70.4%)		435 (70.5%)	
Tobacco use		0.178		0.247		0.908
Non-smoker	374 (59.1%)		349 (67.1%)		331 (68.2%)	
Smoker	54 (55.1%)		54 (72.0%)		53 (70.7%)	
Ex-smoker	123 (53.0%)		110 (71.4%)		95 (66.0%)	

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Table 3. Individual effect of each variable included in multilevel mixed-effects logistic regression models adjusted for paired measures in the 3 trimesters to assess the effect of iodine-rich food intake or supplementation on UIC values ≥150 µg/L

UIC		β coefficient	OR (95%CI)	p
Milk				
	1-2 glasses	-0.464	0.63 (0.48 - 0.82)	0.001
	> 2 glasses	-0.531	0.59 (0.42 - 0.83)	0.002
Yogurt				
	1-2 units	0.134	1.14 (0.80 - 1.63)	0.461
	> 2 units	-0.067	0.94 (0.69 - 1.27)	0.670
Cheese				
	1-2 portions	-0.164	0.85 (0.60 - 1.19)	0.345
	> 2 portions	-0.238	0.79 (0.58 - 1.07)	0.122
Cooked vegetables				
	1-2 portions	-0.510	0.60 (0.36 - 0.99)	0.046
	> 2 portions	-0.581	0.56 (0.34 - 0.91)	0.019
Fresh vegetables				
	1-2 portions	-0.674	0.51 (0.31 - 0.85)	0.009
	> 2 portions	-0.812	0.44 (0.28 - 0.71)	0.001
Fish				
	1-2 portions	-0.363	0.70 (0.44 - 1.09)	0.113
	> 2 portions	-0.358	0.70 (0.44 - 1.10)	0.124
Canned fish				
	1-2 portions	-0.193	0.82 (0.61 - 1.12)	0.212
	> 2 portions	-0.372	0.69 (0.50 - 0.94)	0.021
meet				
	1-2 portions	-0.636	0.53 (0.27 - 1.02)	0.057
	> 2 portions	-0.413	0.66 (0.36 - 1.21)	0.183
Cold cooked meat				
	1-2 portions	-0.100	0.90 (0.66 - 1.23)	0.525
	> 2 portions	0.188	1.21 (0.91 - 1.60)	0.192
Eggs				
	1-2 portions	0.000	1.00 (0.61 - 1.65)	1.000
	> 2 portions	-0.156	0.86 (0.52 - 1.42)	0.545
Fruit				
	1-2 portions	-0.104	0.90 (0.47 - 1.74)	0.757
	> 2 portions	-0.348	0.71 (0.40 - 1.25)	0.232
Dried fruit				
	1-2 portions	-0.221	0.80 (0.64 - 1.00)	0.050
	> 2 portions	0.147	1.16 (0.90 - 1.49)	0.248
Iodized salt				
	yes	-0.726	0.48 (0.40 - 0.59)	0.000
Iodine supplementation				
	yes	-1.035	0.36 (0.29 - 0.44)	0.000
Tobacco use				
	Ex-smoker	0.012	1.01 (0.72 - 1.42)	0.944
	Smoker	0.170	1.19 (0.93 - 1.51)	0.173

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Table 4. Summary of the missing data imputation

Variable	Complete	Imputed	Total
Iodine	2338 (82.5%)	497 (17.5%)	2835
Milk	2341 (82.6%)	494 (17.4%)	2835
Fresh vegetables	2341 (82.6%)	494 (17.4%)	2835
Cooked vegetables	2341 (82.6%)	494 (17.4%)	2835
Canned fish	2341 (82.6%)	494 (17.4%)	2835
Tobacco use	2546 (89.8%)	289 (10.2%)	2835
Iodine supplementation	2341 (82.6%)	494 (17.4%)	2835
Iodized salt	2341 (82.6%)	494 (17.4%)	2835

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Table 5. Results of multilevel mixed-effects logistic regression models adjusted for paired measures in the 3 trimesters to assess the effect of iodine-rich food intake or supplementation on UIC values ≥150 µg/L

A. Multilevel mixed-effects				
Variables	**Coefficient**	**OR(95%CI)**	**p**	**1/OR (95%CI)**
Iodine supplementation	-0.872	0.42 (0.34-0.52)	0.000	2.39 (1.92-2.98)
Iodized salt	-0.403	0.67 (0.54-0.83)	0.000	1.50 (1.21-1.85)
Milk				
1-2 glasses	-0.383	0.68 (0.52-0.90)	0.006	1.47 (1.12-1.93)
>2 glasses	-0.453	0.64 (0.45-0.90)	0.011	1.57 (1.11-2.23)
Constant	0.575			
B. Multilevel with imputation				
Variables	**Coefficient**	**OR(95%CI)**	**p**	**1/OR (95%CI)**
Iodine supplementation	-0.845	0.43 (0.35-0.53)	0.000	2.33 (1.89-2.87)
Iodized salt	-0.383	0.68 (0.55-0.84)	0.000	1.47 (1.19-1.81)
Milk				
1-2 glasses	-0.382	0.68 (0.53-0.88)	0.003	1.46 (1.13-1.89)
>2 glasses	-0.456	0.63 (0.45-0.89)	0.008	1.58 (1.13-2.21)
Constant	0.567			