CLINICAL STUDY

Iodine levels and thyroid hormones in healthy pregnant women and birth weight of their offspring

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Abstract

Introduction: The fetus is most vulnerable to severe iodine deficiency and hypothyroidism during pregnancy. The effects of mild iodine deficiency and subclinical hypothyroidism are poorly known. The present study assesses the association between thyroid hormones (TH)s and urinary iodine concentration (UIC) in healthy pregnant women and the birth weight of their children.

Methods: About 657 pregnant women were recruited in Sabadell and followed until delivery. The association between THs during the first trimester, UIC during the first and third trimesters, and birth weight was studied in 557, 251, and 528 mother–newborn pairs respectively, using linear and logistic regression models adjusted for potential confounders. Only 239 women had all the data available (thyroid function and UIC at the first and third trimesters). Six percent of newborns were classified as small for gestational age (SGA).

Results: The median UIC was 95 and 104 µg/l during the first and third trimesters respectively. Women with the third trimester UICs between 100 and 149 µg/l had lower risk of having an SGA newborn than women with UICs below 50 µg/l (adjusted OR (95%CI): 0.15 (0.03–0.76)). There was no significant reduction in SGA among mothers with higher UICs. Lower free thyroxine and higher TSH levels during the first trimester were not associated with birth weight or SGA. Nevertheless, the analyses were repeated including only those women with all the data available, and high TSH levels became statistically significantly associated with lower birth weight and higher risk of SGA.

Conclusions: The present study suggests that iodine status during pregnancy may be related to prenatal growth in healthy women.

European Journal of Endocrinology 160 423–429

Introduction

Iodine is required for the synthesis of thyroid hormones (TH)s, which are important for the development of the fetus, especially for the maturation of the CN (1). The fetus is dependent on the mother's THs in the early stages of pregnancy, so it is important that pregnant women have adequate TH and iodine levels (2). Iodine deficiency and hypothyroidism during pregnancy have long been known to be associated with neurological deficits and mental retardation (3–5); however, there is also evidence for an increased risk of adverse effects on obstetrical outcomes such as preeclampsia or placental abruption, and negative effects on the offspring such as preterm birth, fetal death, or low birth weight (6–10). Most of the studies that have assessed the effects on reproductive or perinatal outcomes have compared hypothyroid pregnant women to euthyroid pregnant women (6–8, 11–13), pregnant women

living in an iodine-deficient area to pregnant women living in an iodine-sufficient area (9), or iodine-supplemented pregnant women to non-iodine-supplemented pregnant women (14, 15).

The present study was undertaken to assess the association between TH and urinary iodine concentration (UIC) in healthy pregnant women from an area with an unknown iodine status and the birth weight of their children. The objective was to evaluate whether weight at birth may be affected by free thyroxine (T₄) and thyrotropin (TSH) concentrations in the lower and upper limit of the population range respectively as well as the consequences of an iodine deficiency.

Methods

A population-based birth cohort was established in the city of Sabadell (Catalonia, Spain). Between July 2004

and July 2006, 657 pregnant women who visited the public health center of Sabadell for an ultrasound in the first trimester were recruited. Information on education, socioeconomic background, demographic factors, marital status, maternal health and obstetric history, parity, medication use, alcohol and smoking habits during pregnancy, anthropometric measures, and dietary intake were obtained through questionnaires administered during the first and third trimesters of pregnancy. Thyroid function (free T_4 and TSH) was assessed during the first trimester of pregnancy, and UIC was measured at the first and third trimesters. A total of 619 (94%) women were followed until delivery, and anthropometric measures, sex, and gestational age of their children were obtained by specially trained staff and from clinical records. A woman who had a TSH concentration of 126 mU/l and a free T_4 concentration of 0.016 ng/dl ($n=1$), those women who had a thyroid disorder diagnosed ($n=36$), a woman with a child born with some malformations ($n=1$), and women whose children had been born before 34 weeks of gestation ($n=6$) were excluded. In addition, some women had missing data and were also not included in some of the three different analyses (i) free T_4 and TSH versus birth weight, ii) UIC at the first trimester versus birth weight, and iii) UIC at the third trimester versus birth weight). Therefore, 563 mother–newborn pairs (86%) were included in the first analysis, 257 mother–newborn pairs (39%) in the second analysis, and 534 mother–newborn pairs (81%) in the third analysis. More than half of the recruited women had missing data to assess the association between UIC at the first trimester of pregnancy and birth weight, given that we begin to collect urine samples for iodine quantification at half recruitment. Complete data (UIC at the first and third trimesters, thyroid function, birth weight, and covariables) were available in 245 women. Informed consent was signed and the study was approved by the ethics committee of the Institut Municipal d'Investigació Mèdica, Barcelona.

Thyroid hormones and UICs measurement

Thyroid function was assessed during the first trimester of pregnancy by measuring concentrations of TSH and free T_4 in serum samples (Normative Public Health Laboratory of Bilbao, Basque Country, Spain) using a solid-phase, time-resolved sandwich fluoroimmunoassay (AutoDELFIA, PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland) using a lanthanide metal Europium (Eu) label. The between-assay coefficients of variation (CVs) at three levels of hormone concentration were 3.0, 3.1, and 2.6% for low, medium, and high concentrations of TSH respectively, and 6.1, 4.1, and 4.0 for free T_4 . The intra-assay CVs were 7.7, 2.1, and 1.7% for TSH, and 3.7, 3.0, and 3.3% for free T_4 . UICs were measured in single spot urine samples in a total of 303 and 600 pregnant women during the first and third trimesters of pregnancy respectively,

using paired-ion reversed-phase high-performance liquid chromatography with electrochemical detection and a silver working electrode. Samples were stored at -20°C prior to the analyses.

Birth weight

Birth weight was studied both as a continuous variable and as a dichotomous variable based on small size (weight) for gestational age. Small for gestational age (SGA) was used as a definition for intrauterine growth restriction to identify those children whose birth weight was below the 10th percentile of the distribution for the corresponding gestational age according to Spanish reference tables from Carrascosa *et al.* (16). Additionally, a new definition for growth restriction based on failing to achieve their growth potential (17) was also used to better distinguish intrauterine growth restriction from constitutionally small infants (i.e., with parents of small stature). Fractional polynomial model was used to predict birth weight taking into account maternal and newborn characteristics (gestational age as inverse of square, sex, interaction of sex and gestational age, maternal age height and weight, and parity). We developed an adjusted SGA variable (SGAadj), which considered as SGA infants only those newborns classified as small in the two definitions ($n=32$), and excluded infants classified as SGA using the Spanish reference tables, but whose birth weight exceeded the 10th percentile of predicted values ($n=6$). Therefore, 557, 251, and 528 mother–newborn pairs were finally included in the subsequent analysis to assess the effects of thyroid function, UIC at the first trimester, and UIC at the third trimester respectively, and only 239 women had complete data (all measurements). Children classified as large for gestational age (LGA) ($n=59$) were included in the analysis; however, the analyses were repeated excluding these newborns and results were compared.

Statistical analysis

The population was classified into five groups according to their UICs: i) $<50\text{ }\mu\text{g/l}$, ii) $50\text{--}100\text{ }\mu\text{g/l}$, iii) $100\text{--}150\text{ }\mu\text{g/l}$, iv) $150\text{--}249\text{ }\mu\text{g/l}$, and v) $>250\text{ }\mu\text{g/l}$ based on the WHO classification (18) in order to examine the linearity of the relationship between UIC and the outcomes. Free T_4 and TSH were categorized using the 10th and 90th percentiles respectively. The association between free T_4 , TSH, and UIC (as categorical variables) and birth weight (as the dichotomous and continuous variable) was evaluated using logistic and linear regression. Models were adjusted for time of day, gestational age, and season at sampling, mother's smoking habits, mother's age, weight and height, infant's sex, and nulliparity (when using adjusted SGA as the outcome). Models using birth weight as a continuous outcome were also adjusted for gestational

Table 1 Thyroid hormones and urinary iodine concentrations (UIC) in pregnant women.

	<i>n</i>	Percentiles		
		25th	50th	75th
First trimester				
Free T ₄ (ng/dl)	557	0.76	0.82	0.89
TSH (mU/l)	557	0.80	1.18	1.75
Urine iodine (µg/l)	251	56	95	154
Third trimester				
Urine iodine (µg/l)	528	64	104	161

age at delivery. Models were also repeated using the SGA variable strictly defined with the Spanish reference tables from Carrascosa (16), thus including those six children excluded in the adjusted SGA variable. TSH showed a non-normal distribution and was log-transformed to study the relationship between the different categories of UIC at the first trimester and TSH. Statistical significance was set at a *p*-value < 0.05. All analyses were conducted with the STATA 8.2 statistical software package.

Results

Median UIC in the population studied was 95 and 104 µg/l during the first and third trimesters respectively (Table 1).

UIC both at the first and third trimesters was available in 243 mother–newborn pairs. A statistically significant association was observed between UIC in the first and third trimesters as continuous variables (Spearman correlation: 0.24, *p*-value < 0.001), although only 25% (*n* = 61) of the women with UIC at the first and third trimesters available were in the same category of UIC in both trimesters (Table 2). About 48% of women (*n* = 117) increased their UIC category and 27% decreased their UIC category (*n* = 65) between the first and third trimesters. Ten women with UIC below 50 µg/l remained low in the third trimester.

The mean birth weight and height were 3259 g and 49 cm respectively. Fifty-one percent of the children included were males (Table 3). After excluding those children who were born before 34 weeks of gestation, there were still 13 newborns with less than 37 weeks of gestation, also considered to be preterm. The mean age,

weight, and height of pregnant women were 31 years, 62.3 kg, and 163 cm respectively. Sixteen percent of the women smoked during pregnancy, and 57% were nulliparous. About 10 and 11% of the women used iodized salt at the first and third trimesters respectively. About 6 and 8.6% of women used iodine supplements during the first and third trimesters of pregnancy, either as iodine or multivitamin tablets containing between 100 and 200 µg of iodine each.

Six percent of infants were classified as SGA. When infants were categorized according to UIC levels during pregnancy, the lowest rates of SGA were observed among those whose mothers had UICs between 100 and 149 µg/l either in the first or third trimester, as well as among those with UICs above 249 µg/l in the first trimester (Table 4). The highest rate of SGA was observed in children whose mothers had UICs below 50 µg/l in the third trimester (10%). Small differences in median birth weight were seen among groups, with the highest median birth weight observed among infants whose mothers had UICs between 100 and 149 µg/l in either the first or third trimester.

In the multivariate model, women with UICs between 100 and 149 µg/l in the third trimester had the lowest risk of having an SGA infant, and their babies had higher mean birth weights than those with UICs below 50 µg/l (Table 5). Birth weights among women with UICs between 50 and 99 µg/l in the third trimester were also significantly higher than those among women with UICs below 50 µg/l. However, for women with UICs in categories above 150 µg/l, the increase in adjusted mean birth weight and the reduced probability of having an SGA infant did not reach significance. UICs at the first trimester showed similar findings than UICs at the third trimester, particularly for birth weight, although differences were not statistically significant. Free T₄ and TSH measured during the first trimester were not associated with birth weight. When models were repeated using the classical SGA outcome, a decreased risk of having a small baby was again observed only in those women with UICs between 100 and 149 µg/l (OR (95%CI): 0.27 (0.08–0.98)) at the third trimester. Associations between thyroid function and UICs at the first and third trimesters did not change after excluding those children classified as LGA (data not shown).

Table 2 Distribution of pregnant women according to the urinary iodine concentrations (UIC) at the first and third trimesters (*n* (%)).

	UIC (third trimester)				
	< 50 µg/l	50–99 µg/l	100–149 µg/l	150–249 µg/l	> 249 µg/l
UIC (first trimester)					
< 50 µg/l	10 (20)	18 (36)	10 (20)	9 (18)	3 (6)
50–99 µg/l	8 (10)	22 (28)	22 (29)	17 (22)	8 (10)
100–149 µg/l	4 (8)	14 (29)	10 (20)	15 (31)	6 (12)
150–249 µg/l	0 (0)	10 (21)	13 (27)	15 (31)	9 (19)
> 249 µg/l	1 (5)	6 (30)	6 (30)	3 (15)	4 (20)

Table 3 Characteristics of the study population.

Newborn variables (<i>n</i> =557)		
Sex (% males)		50.81%
Gestational age ^a (weeks)		40 (1.4)
Premature (% < 37 weeks)		3.2%
Birth weight ^a (g)		3259 (420)
Birth height ^a (cm)		49 (1.9)
Maternal variables (<i>n</i> =557)		
Age ^a (weeks)		31 (4.3)
Weight ^a (g)		62.3 (11.8)
Height ^a (cm)		163 (6)
Race (% white)		97%
Smoking during pregnancy (% yes)		16%
Studies (%)		
Primary or less than primary		28%
Secondary		43%
High		29%
Nullipara (%)		57%
Characteristics at sampling	First trimester (<i>n</i> =251)	Third trimester (<i>n</i> =528)
Gestational age ^a (weeks)	13 (1.7)	34(1.4)
Time (%)		
Before 1000 h	31%	31%
1000–1200 h	44%	51%
1200–1400 h	6%	13%
After 1400 h	19%	6%
Station (%)		
Winter	22%	27%
Spring	23%	25%
Summer	27%	25%
Autumn	28%	23%
Use of iodized salt	10%	11%
Iodine supplementation (%)	6.4%	8.6%

^aCharacteristic described as mean (S.D.)

Associations observed between UIC and SGAadj/ birth weight were similar when models were repeated in the subset of women who had all the measurements available (free T₄, TSH, and UICs at the first and third trimesters; Table 6). However, high TSH levels become statistically significantly related to an increase in the risk of having a small baby and lower birth weight. Moreover, the odds ratio for the category of women with UIC between 100 and 149 µg/l was not statistically significant, although this category had again the lowest odds ratio in both the trimesters.

The adjusted association between TSH and T₄ and the different categories of UIC (first trimester) is shown in Table 7. A linear relationship is not observed between the different categories of UIC and TSH or T₄; however, those women with UIC between 100 and 149 µg/l had lower levels of TSH (adjusted coefficient: −0.36 (0.15) mU/l log-TSH) and higher levels of T₄ (adjusted coefficient (S.E.M.): 0.05 (0.02) ng/dl) than those with the UIC below 50 µg/l. Moreover, those women with UIC between 50 and 99 µg/l had also higher levels of T₄ than those women from the reference category. Among the other UIC categories, there were no differences on free T₄ and TSH.

Discussion

We observed that healthy pregnant women with the third trimester UICs below 50 µg/l were significantly more likely to have an SGA infant than women with the UICs between 100 and 149 µg/l and their infants had a lower mean birth weight than women with the UIC between 50 and 149 µg/l. A similar pattern was seen for UIC at the first trimester, although differences were not statistically significant. Higher TSH levels were also associated with a higher risk of having an SGA baby or having a newborn with a lower birth weight; nonetheless, this association was observed only when women with all the measurements were analyzed.

The best-established association between THs, iodine, and anthropometric measures is in school and pre-school children, generally from iodine-deficient areas where retarded growth has been observed (15, 19). Thyroid hormone plays a key role in growth and bone development either indirectly by increasing the secretion of GH and insulin-like growth factor 1, or directly by influencing target genes via specific nuclear receptors (20, 21). It is well known that the disruption of the hypothalamic–pituitary–thyroid axis during growth profoundly influences skeletal development (22). The expression of TH receptors in bone cells as

Table 4 Percentage of small for gestational age (adjusted SGA) infants and median interquartile range birth weight according to free thyroxine (fT₄), thyrotropin (TSH), iodine supplementation, and urinary iodine concentrations (UIC) in pregnant women.

	<i>n</i>	SGAadj (%)	Birth weight median (IQR) ^a
All population	557	6.0	3290 (2980–3520)
First trimester			
Free T ₄			
> PC10	501	6.2	3290 (2990–2010)
< PC10	56	3.6	3350 (3035–3580)
TSH			
< PC90	501	5.8	3300 (3000–3520)
> PC90	56	7.0	3185 (2860–3500)
UIC			
UIC < 50 µg/l	50	4.0	3257 (2960–3500)
UIC 50–99 µg/l	82	6.1	3312 (3020–3640)
UIC 100–149 µg/l	50	2.0	3375 (3060–3530)
UIC 150–249 µg/l	49	6.1	3300 (3080–3510)
UIC > 249 µg/l	20	0.0	3350 (2980–3460)
Iodine supplementation			
No	523	6.3	3290 (2990–3520)
Yes	34	0.0	3285 (2980–3515)
Third trimester			
UIC			
UIC < 50 µg/l	70	10.0	3162 (2820–3430)*
UIC 50–99 µg/l	182	6.0	3300 (2990–3550)
UIC 100–149 µg/l	126	1.6	3350 (3010–3620)
UIC 150–249 µg/l	101	5.9	3290 (3030–3460)
UIC > 249 µg/l	49	8.2	3280 (3015–3630)
Iodine supplementation			
No	510	6.5	3285 (2980–3515)
Yes	47	0.0	3370 (3080–3645)*

**P* < 0.05 (χ², Mann–Whitney and ANOVA tests).^aIQR: interquartile range.

Table 5 Adjusted association between urinary iodine concentration, thyrotropin (TSH), thyroxine (T_4), and fetal weight, using the fetal weight as a dichotomous outcome (small for gestational age (SGA)) and as a continuous variable.

	Small for gestational age (SGAadj) Adjusted ^a odds ratio (95% CI)	Birth weight (g) Adjusted ^b coefficient (S.E.M.)
First trimester		
Free T_4 (<PC10)	0.58 (0.13–2.67)	67 (54)
TSH (>PC90)	1.31 (0.41–4.17)	–19 (52)
UIC		
UIC <50 µg/l	1	3457 (113)
(Reference)		
UIC 50–99 µg/l	1.73 (0.24–12.56)	123 (69)
UIC 100–149 µg/l	0.37 (0.03–5.36)	133 (76)
UIC 150–249 µg/l	1.34 (0.16–12.06)	78 (76)
UIC >249 µg/l	Not measurable ^c	142 (102)
Third trimester		
UIC		
UIC <50 µg/l	1	3506 (207)
(Reference)		
UIC 50–99 µg/l	0.59 (0.21–1.69)	117 (51)*
UIC 100–149 µg/l	0.15 (0.03–0.76)*	189 (54) [†]
UIC 150–249 µg/l	0.37 (0.10–1.40)	106 (57)
UIC >249 µg/l	0.71 (0.19–2.75)	99 (67)

* P value < 0.05, [†] P value < 0.001.^aAdjusted for time, gestational age and season at sampling, mother's smoking habits (reference: no smoking), mother's age (31 years), weight (63 kg) and height (163 cm), sex (male), and nulliparity (nulliparous).^bAdjusted for gestational age at delivery (40 weeks).^cOR not measurable (this category of UIC predicts failure perfectly).

the responsiveness to TH in cell culturing systems is the evidence of an effect of TH on bone tissue (21–23). However, the importance of TH during the prenatal development is uncertain (15, 23) and a very few studies have assessed the role of iodine on prenatal growth (14, 15). A recent study in animals showed that hypothyroidism in pregnant mice impaired fetal bone development, but only at the end of fetal life (23). In the present study, the UIC levels during the third trimester of pregnancy were related to birth weight. Nonetheless, no statistically significant relationship was observed for the first trimester UICs and TH.

By convention, standard reference ranges for adults are used during pregnancy, although Hallowell *et al.* proposed a TSH upper limit of 2.5 mU/l as a conservative upper guide for the first trimester pregnancy screening. (24). In the present study, we did not observe any adverse effect of high TSH (TSH > 2.42 mU/l) or low free T_4 concentrations (free T_4 < 0.70 ng/dl) on birth weight when all women were considered. Nevertheless, when only women with all the measurements available were analyzed, we observed that high TSH levels were related to a higher risk of SGA and lower birth weight. It is known that UI concentration does not always provide direct information about thyroid function (25, 26); however, we also found that women whose UICs were within 100 and 149 µg/l during the first trimester also had lower levels of TSH and higher levels of free T_4 than women with UIC below

50 µg/l. This pattern was not observed in women with higher UIC levels.

UIC is presently the most practical biomarker for assessing iodine nutrition in a population, although not in individuals since it reflects recent iodine intake (27). Nevertheless, low UI levels probably reflect a prolonged low iodine status in an individual (26). Three methods have been used to estimate daily iodine requirements in adults: 1) iodine turnover, 2) iodine balance, and 3) UI concentration and thyroid size (28). The iodine requirements during pregnancy increase since there is an increment in TH synthesis to provide for the needs of the fetus, and there is an increased loss of iodine in the urine resulting from an increased renal clearance during pregnancy (2, 28, 29). The recommended iodine intake in pregnant women, at the moment 250 µg per day, has been mainly extrapolated from the non-pregnant adult estimations (for whom the recommended level is 150 µg/day), and it is thus essentially based on theoretical considerations (18, 29). Given the increased needs and elevated excretion rates, there is a need to empirically validate the recommended median UI in pregnant women in relation to the consequences for reproductive outcomes as well as longer term outcomes such as child development, maternal goiter, or thyroid autoimmunity. Moreover, it is important to clarify whether an increase in iodine intake is required among pregnant women

Table 6 Adjusted association between urinary iodine concentration, thyrotropin (TSH), thyroxine (T_4), and fetal weight, using the fetal weight as a categorical outcome (small for gestational age) and as a dichotomous variable. Only women with all measurements available were included ($n=239$).

	Small for gestational age (SGAadj) Adjusted ^a odds ratio (95% CI)	Birth weight (g) Adjusted ^{a,b} coefficient (S.E.M.)
First trimester		
Free T_4 (<PC10)	0.70 (0.07–6.89)	–16 (71)
TSH (>PC90)	8.29 (1.59–43.2)*	–182 (81)*
UIC		
UIC <50 µg/l	1	Reference
(Reference)		
UIC 50–99 µg/l	1.79 (0.25–12.97)	108 (69)
UIC 100–149 µg/l	0.38 (0.03–5.45)	131 (76)
UIC 150–249 µg/l	1.54 (0.17–13.77)	83 (77)
UIC >249 µg/l	Not measurable ^c	141 (102)
Third trimester		
UIC		
UIC <50 µg/l	1	Reference
(Reference)		
UIC 50–99 µg/l	0.50 (0.06–3.80)	123 (86)
UIC 100–149 µg/l	0.20 (0.01–2.82)	201 (88)*
UIC 150–249 µg/l	0.63 (0.07–5.45)	89 (90)
UIC >249 µg/l	0.64 (0.06–6.33)	55 (100)

* P value < 0.05.^aAdjusted for time, gestational age and season at sampling, mother's smoking habits (reference: no smoking), mother's age (31 years), weight (63 kg) and height (163 cm), sex (male), and nulliparity (nulliparous).^bAdjusted for gestational age at delivery (40 weeks).^cOR not measurable (this category of UIC predicts failure perfectly).

Table 7 Adjusted^a association between thyroxine (T₄), thyrotropin, and urinary iodine concentrations (UIC) at the first trimester (n=251).

	n	Adjusted ^a coefficient (S.E.M.)	
		TSH ^b (mU/l)	T ₄ (ng/dl)
UIC (first trimester)			
UIC <50 µg/l	50	Reference	Reference
UIC 50–99 µg/l	82	–0.07 (0.14)	0.05 (0.02) [†]
UIC 100–149 µg/l	50	–0.36 (0.15)*	0.05 (0.02)
UIC 150–249 µg/l	49	–0.16 (0.15)	0.02 (0.02)
UIC >249 µg/l	20	–0.09 (0.21)	0.00 (0.03)

[†]P value <0.01, *P value <0.05.
^aAdjusted for mother's weight and age, gestational age at sampling, and mother's smoking habits.
^bTSH was log-transformed to normalize the distribution.

from iodine-sufficient areas, since physiological adaptations in iodine metabolism take place among women with adequate iodine intake before pregnancy (30). It is possible that recommending an increase in iodine intake during pregnancy may be excessive in these populations.

Iodine status in the pregnant women of the present study would be considered inadequate based on the present WHO criteria (18). Some parts of Spain have had historical problems of endemic goiter described during the 1970s and 1980s; however, the situation improved after information campaigns for eradicating iodine deficiency (31).

The major disadvantage of the present study is the use of UIC as an indicator of individual iodine status, although a categorization in five different groups according to UIC instead of using the continuous measure diminishes the possible misclassification bias due to daily variations of iodine intake. Unfortunately, not all pregnant women had UICs analyzed at both trimesters because of budget restrictions, thus separate analyses were done for each trimester, and a decreased risk of SGA was observed in women with UICs between 100 and 149 µg/l during either the first or third trimester (although only statistically significant at the third trimester), which reinforces the association. Moreover, there is likelihood that women with higher UIC had also a higher daily intake of energy or of other nutrients beneficial for fetal growth, although the effect of UIC did not change after the adjustment for total calories intake. Other disadvantages were the missing information on the prevalence of positive TPOAb in the present population and on thyroxin binding globulin (TBG) concentrations to calculate the free T₄/TBG ratio. Thyroid autoimmunity, which is the most common cause of subclinical hypothyroidism in iodine-sufficient areas, influences TSH levels and also plays a critical role in pregnancy outcome (32). Moreover, some TH variations observed during pregnancy (for instance, a decrease of free T₄ levels) are the direct consequence of an increase in serum TBG (33). Multivariate models

were adjusted for gestational age at sampling to reduce the possible bias due to variations during gestation.

In conclusion, we have observed an association between thyroid function, iodine status, and prenatal growth. This study suggests a beneficial effect on birth weight at UIC below the present recommendations. Further studies should be undertaken to assess the effects of moderate-to-mild iodine deficiency and iodine excess during pregnancy, as well as to validate the present guidelines in relation to reproductive and long-term outcomes in both iodine-deficient and -sufficient areas.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This study was funded by grants from the Spanish Ministry of Health (FIS-FIS-PI041436), Instituto de Salud Carlos III (Red INMA G03/176 and CB06/02/0041), and the Generalitat de Catalunya-CIRIT 1999SGR 00241.

Acknowledgements

We are grateful to Silvia Fochs, Anna Sànchez, Maribel López, and Nuria Pey for their assistance in contacting the families and administering the questionnaires.

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Received 5 December 2008

Accepted 29 December 2008