Maternal Urinary Iodine Concentration up to 1.0 mg/L Is Positively Associated with Birth Weight, Length, and Head Circumference of Male Offspring1,2

Filip Rydbeck, 3 Anisur Rahman, 4 Margaretha Grandén, 3 Eva-Charlotte Ekström, 5 Marie Vahter, 3 and Maria Kippler 3*

3Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden; 4Centre for Reproductive Health, International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh; and 5Department of Women’s and Children’s Health, International Maternal and Child Health, University Hospital, Uppsala, Sweden

Abstract

Adequate iodine status in early life is crucial for neurodevelopment. However, little is known about the effects of maternal iodine status during pregnancy on fetal growth. The present study investigated the potential impact of maternal iodine status during pregnancy on offspring birth size. This large prospective cohort study was nested in a Bangladeshi population-based randomized supplementation trial in pregnant women [MINIMat (Maternal and Infant Nutrition Interventions in Matlab)]. Urine samples obtained at 8 wk of gestation from 1617 women were analyzed for iodine and other elements, such as arsenic and cadmium, using inductively coupled plasma mass spectrometry. Anthropometric measurements at birth included weight, length, and head and chest circumference. Maternal urinary iodine concentrations (UICs) ranged from 0.020 to 10 mg/L, with a median of 0.30 mg/L. Below 1.0 mg/L, UIC was significantly positively associated with birth weight and length. Birth weight and length increased by 9.3 g (95% CI: 2.9, 16) and 0.042 cm (95% CI: 0.0066, 0.076), respectively, for each 0.1-mg/L increase in maternal UIC. No associations were observed between UIC and head or chest circumference. When we stratified the analyses by newborn sex, the positive associations between maternal UIC (<1 mg/L) and measurements of size at birth were restricted to boys, with no evidence in girls. Among boys, the mean weight, length, and head circumference increased by 70 g (P = 0.019), 0.41 cm (P = 0.013), and 0.28 cm (P = 0.031) for every 0.5-mg/L increase in maternal UIC. Maternal iodine status was positively associated with weight, length, and head circumference in boys up to ~1 mg/L, which is well above the recommended maximum concentration of 0.5 mg/L. The associations leveled off at UIC ≥ 1 mg/L. Our findings support previous conclusions that the advantages of correcting potential iodine deficiency outweigh the risks of excess exposure. J. Nutr. 144: 1438–1444, 2014.

Introduction

Iodine is a critical component of thyroid hormones, which in turn are essential for controlling metabolic rate, development of body structures, and neuronal maturation (1,2). A woman’s iodine requirement increases markedly during pregnancy to do the following: 1) maintain thyroid hormone concentrations despite a pregnancy-related increase in renal clearance of iodine; 2) supply the fetus with thyroxine in the first trimester before it can produce its own; and 3) supply the fetus with iodine later in pregnancy for its own thyroid hormone production (3).

Iodine deficiency is a major health concern for pregnant women and their children. The WHO recommends a daily iodine intake of 0.25 mg for pregnant women compared with 0.15 mg for other adults (2,4). However, a median urine concentration of 0.25–0.49 mg/L is associated with an iodine intake above required amounts, and ≥0.5 mg/L is associated with excessive iodine intake and may have adverse effects on fetal development (2).

The importance of adequate iodine status for early-life neurodevelopment was demonstrated (5,6). However, little is known about potential effects of maternal iodine status on fetal growth. In a prospective Spanish study (n = 528), iodine-deficient...
mothers [urinary iodine concentrations (UICs) < 0.050 μg/L] had a higher risk of giving birth to small-for-gestational-age babies (adjusted OR: 0.15; 95% CI 0.03, 0.76) compared with mothers with a UIC of 0.10–0.15 mg/L (7). However, a smaller study from Argentina (n = 77) showed that a maternal UIC > 0.15 mg/L did not influence newborn weight compared with a lower UIC (8). We reported recently that, according to UICs measured 4 times throughout pregnancy, women in a rural area in Bangladesh generally had adequate or more than adequate iodine intake (9).

The aim of the present prospective, large cohort study was to assess the impact of maternal iodine status during pregnancy on newborn size at birth.

Material and Methods

Study area and design. The present prospective cohort study is part of our ongoing research on long-term effects of various early-life environmental factors on child health and development (10,11). The cohort was nested in a randomized population-based food and micronutrient supplementation trial during pregnancy [MINIMat (Maternal and Infant Nutrition Interventions in Matlab)] (12,13) in a rural area located ~50 km southeast of Dhaka, Bangladesh. In Matlab, the International Centre for Diarrhoeal Disease Research, Bangladesh operates a central hospital with 4 connected health care facilities, as well as a health and demographic surveillance system (HDSS) with community research health workers visiting the households on a monthly basis (12). At these visits, the HDSS workers offered a urine pregnancy test (ACON) to all women who reported that their menstruation was overdue. If the test was positive, the woman was asked to donate a urine sample [on average, at gestational week (GW) 8] for exposure assessment and was referred to the nearest health care facility for ultrasound examination and screening for eligibility in the supplementation trial (viable fetus, gestational age < 14 wk, no severe maternal illnesses). The women were randomly assigned to food supplementation (starting in early- or mid-pregnancy), and 1 of 3 different micronutrient supplementations (starting at GW14): 1) 30 mg/d iron and 400 μg/d folic acid; 2) 60 mg/d iron and 400 μg/d folic acid; or 3) a preparation of 15 micronutrients (12,14), including 0.15 mg of iodine (potassium iodide).

In total, 4436 women were enrolled in the MINIMat trial from November 2001 through October 2003 (12). For the present study, we considered all women who were recruited during 1 full calendar year (February 2002 through January 2003) irrespective of micronutrient treatment group and who gave birth to a single child with size measurements taken at birth (n = 1697) (15). Of those, 1617 (95%) provided a spot urine sample at the time of pregnancy testing for measurement of iodine and other elements.

The study was approved by the ethics committee at both the International Centre for Diarrhoeal Disease Research, Bangladesh and the Karolinska Institute (Stockholm, Sweden). Consent was obtained from all women, and they were free to refrain from any part of the study at any time.

Laboratory analysis of urinary iodine. Maternal iodine status was assessed by UIC as recommended by the WHO (2). Spot urine samples were collected into urine collection cups and transferred to 24-mL polyethylene bottles (Zinsser Analytic), which were stored at ~70°C. UIC was measured using inductively coupled plasma MS (Agilent 7700; Agilent Technologies) after dilution with ammonium. Procedures, including quality control, were described in detail previously (9). All of our samples contained an iodine concentration above the limit of detection (0.5 μg/L). All concentrations were adjusted for the specific gravity, measured with a digital refractometer (EUROMEX RD712 Clinical Refractometer) to compensate for the variation in urine dilution (16). Mean specific gravity at GW8 was 1.012 g/mL.

Outcomes and covariates. Birth weight was measured with electronic or beam scales (UNICEF; Uniscale; SECA), length with a locally produced wooden collapsible length board, and head and chest circumferences with a flexible nonstretchable measuring tape (15). For deliveries at health facilities, anthropometric measurements were conducted by the attending nurse, whereas children delivered at home (~60%) were measured mostly within 72 h by trained health workers. Measurements conducted >72 h after birth were adjusted as described previously (12). Gestational age at birth was based on the date of the last menstrual period. For women who were uncertain of the date of their last menstrual period, gestational age was estimated by ultrasound measurements (15). Season of birth was categorized as pre-monsoon (January to May), monsoon (June to September), and post-monsoon (October to December).

Data on maternal characteristics were obtained from either the MINIMat trial or the HDSS database. Maternal height and weight were recorded at enrollment and used to calculate the maternal BMI [weight (kg)/height (m2)]. Education, defined as years at school, was categorized by median split (<5 and ≥5 y). Socioeconomic status (SES) was estimated via an asset index (15,17).

We showed previously that the women, although living in an non-industrialized rural area, are exposed to varying amounts of inorganic arsenic (mainly through drinking water) and cadmium (through food) and that these exposures [based on urinary concentrations at GW8] are associated with decreased fetal growth (15,18,19). Thus, we included urinary concentrations of arsenic and cadmium as covariates. Other factors known to affect fetal size include alcohol, tobacco smoking, and betel quid chewing (20,21). We only accounted for betel quid use during pregnancy (defined as never or ever used) because none of the women drank alcohol and only 2 women (<0.1%) reported tobacco smoking during pregnancy.

Statistical analyses. The statistical analyses were performed using STATA (version 11; StataCorp). All tests were 2-sided, with P < 0.05 considered statistically significant. Initially, all associations between maternal UIC and the different outcomes were examined visually using scatter plots with Lowess moving-average fitted curves. Because the associations appeared to be nonlinear, we applied a linear spline model with knot at 1.0 mg/L, as indicated in the plots (Fig. 1A–D). We adjusted for covariates that were associated with either maternal UIC or the outcomes (P < 0.05) or were shown previously to influence the outcomes. These associations were assessed using either the Spearman rank correlation (continuous variables) or the Mann-Whitney U test (comparing 2 independent groups). Collinearity, evaluated by tolerance and the variance inflation factor, was apparent for age and parity (r = 0.60) and for education and SES (r > 0.64). We only included parity and level of formal education into the models, because these variables resulted in the strongest regression coefficients.

We created 3 different multivariable-adjusted linear spline models. Model I was adjusted for maternal BMI, parity, level of formal education, season of birth, gestational age at birth (<37 and ≥37 wk), and newborn sex. Model II was additionally adjusted for the food and micronutrient supplementation (6 groups). In Model III, we removed supplementation and added betel quid chewing habits, along with maternal urinary cadmium and arsenic metabolites. We tested to include both SES and education in the models using sensitivity analysis. In addition, we excluded gestational age from Model I because it may have inhibited exposure to effects. Finally, we stratified the multivariable-adjusted linear regression analyses (Model I, <1.0 mg/L) by newborn sex.

To explore whether the impact of maternal iodine intake during pregnancy on anthropometry measures at birth differed between smaller (25th percentile; lowest quantile of all size-at-birth measurements), normal (50th percentile; median quantile), and larger (75th percentile; highest quantile) newborns, we also performed multivariable-adjusted quantile regression analyses (adjusted as in Model I). All regression coefficients, corresponding CIs, and P values were based on 200 bootstrap samples. We used the Wald test to evaluate potential differences between the quantile-specific regression coefficients.
Finally, we evaluated the risk of preterm delivery (<37 wk of gestation) and term low birth weight (<2260 g, i.e., 10th percentile of all born at least at GW37) in relation to UIC (quartiles) using multivariable-adjusted logistic regression analysis. We adjusted as in Model I, excluding gestational age at birth. Linear trends across categories were assessed using the median UIC within categories as a continuous variable.

**Results**

The median UIC at GW8 was 0.30 mg/L (mean of 0.44 mg/L) with a wide overall range of 0.0020–10 mg/L (10–90th percentiles: 0.084–0.99 mg/L). Only 2 women (<0.1%) reported that they smoked during pregnancy, and only 1 of them smoked on a daily basis. Mothers in the lowest quartile of UIC were less educated, had lower SES, and were more prone to undernourishment in early pregnancy (BMI < 18.5 kg/m²) (Table 1). They also had higher concentrations of cadmium and arsenic compared with mothers in the highest quartile but used betel quid (with or without tobacco) slightly less often. Both preterm delivery (younger than GW37) and low birth weight (<2500 g) were more common among mothers in the lowest UIC quartiles compared with those in the higher quartiles (Table 1).

In general, the birth size measurements increased linearly with increasing maternal UIC up to ~1.0 mg/L (Fig. 1A–D), after which the association leveled out. Applying a linear spline model (spline knot at 1.0 mg/L) (Table 2, Crude), we found that a maternal UIC < 1.0 mg/L was positively associated with all the outcomes. After adjusting for covariates (Table 2, Model I), maternal UIC < 1.0 mg/L was significantly positively associated with birth weight and length. The birth weight and length increased by 47 g (95% CI: 14.5, 80; \(P < 0.0040\)) and 0.21 cm (\(P < 0.020\)), respectively, for every 0.50-mg/L increase in maternal UIC (WHO cutoff for excess exposure). No association was observed between UIC and birth weight at UIC \(\geq 1.0\) mg/L, whereas a suggested weak inverse association was observed with length (\(P = 0.10\)). Furthermore, the regression slopes relating UIC with weight and length were significantly different when comparing UIC of <1.0 and \(\geq 1.0\) mg/L (Wald test, \(P = 0.023\) and 0.014, respectively). Additional adjustments for the food and micronutrient supplementation (Table 2, Model II) or maternal betel quid chewing and exposure to cadmium and arsenic (Table 2, Model III) had marginal effects on the effect estimates.

In sensitivity analyses, neither SES nor education changed the estimates (data not shown). Exclusion of gestational age at birth in Model I increased the effect estimates of UIC < 1.0 mg/L in relation to birth weight by 29% (\(B = 12; 95\% CI: 5.0, 19; P = 0.001\)) and length by 29% (\(B = 0.059; 95\% CI: 0.020, 0.098; P = 0.0030\)). The effect estimates of UIC \(\geq 1.0\) mg/L remained practically unchanged (data not shown).

The risk of preterm delivery tended to decrease with increasing maternal UIC (adjusted as in Model I, except for gestational age at birth), although the association was not statistically significant (OR: 0.65; 95% CI: 0.37, 1.13) when comparing the highest UIC quartile (26 cases) with the lowest (36 cases; \(P\)-trend = 0.065). The ORs for term low birth weight was 0.74 (95% CI: 0.43, 1.27) when comparing the highest UIC quartile (30 cases) with the lowest (37 cases; \(P\)-trend = 0.13), sex; and \(\delta\) gestational age at birth (<37 and \(\geq 37\) wk). The total number of observations was 1616; 1 woman with a urinary iodine concentration of 10 mg/L was excluded from the figures. GW, gestational week.
Additional adjustment for gestational age at birth (≥37–40 and ≥40 wk) resulted in an OR of 0.79 (95% CI: 0.46, 1.36; P-trend = 0.22).

Stratification by newborn sex (adjusted as in Model I, except for sex) showed positive associations between maternal UIC (<1.0 mg/L) and birth weight, length, and head circumference in boys but not girls (Fig. 2A). Among the boys, a 0.50-mg/L increase in maternal UIC corresponded with an increase in mean birth weight, length, and head circumference of 70 g (P = 0.019), 0.41 cm (P = 0.013), and 0.28 cm (P = 0.031), respectively.
Birth weight has been divided by 100 to fit the scale of the figure. Q, regression analyses were additionally adjusted for newborn sex, season of birth, and gestational age, and maternal urinary iodine concentration using quantile regression analyses (including all newborns of women of birth weight, length, and head and chest circumference obtained after stratification of linear regression analyses by newborn sex). The observed fairly modest increase in birth weight over the wide range of maternal UIC is in contrast to the main previous study in which the 10th percentile was 0.084 mg/L.

We did not observe any clear adverse effect on size at birth at UIC > 1.0 mg/L (Fig. 1A–D). According to recent evaluations, most pregnant women maintain normal thyroid function with high iodine intakes, and only those with subtle defects in thyroid hormone synthesis may be unable to recover from the acute inhibition that occurs with excessive intake (26,27). However, excess iodine intake during pregnancy might increase the risk of fetal hypothyroidism because the fetal thyroid is not mature until the last month of pregnancy (26). To reduce the risk of hyperthyroidism, the WHO recommends that pregnant women avoid iodine intakes >0.25 mg/d if the iodine intake increases rapidly after long-term deficiency (5). The main source of iodine in rural Bangladesh is table salt, because iodine fortification of table salt has been mandatory since 1989 in Bangladesh (24). The extensive variation in UIC that we found is likely related to poor control of fortification homogeneity, along with loss of salt iodine by evaporation due to the warm climate (28,29). Another important, but essentially neglected, source of iodine is drinking water, which has a median iodine concentration of 0.14 mg/L in deeper wells according to our previous research (overall median of 0.0030–0.44 mg/L) (9). Assuming a water consumption of 2–3 L/d, drinking water may constitute an important source of iodine. That might also explain the lower UIC observed during the monsoon season (median of 0.18 mg/L) (25), which is in sharp contrast to the present study in which the 10th percentile was 0.084 mg/L.

The mechanisms behind the positive effect of prenatal iodine status on birth size in boys, but not girl, are not known. To our knowledge, no previous data showed sex-specific effects of iodine on fetal growth. However, the proportion of neonatal blood thyroid-stimulating hormone concentrations above the WHO cutoff for estimated iodine sufficiency is higher for male than for female newborns, especially in those with low birth weight (31,32). Additionally, male fetuses grow more rapidly than do female ones in late gestation, which may increase their susceptibility to malnutrition compared with females (33). Although the effect was mediated partly through the lower risk of preterm birth, we cannot entirely exclude the possibility of

In the multivariable-adjusted quantile regression analyses (<1.0 mg/L; adjusted as in Model I), we found fairly similar associations across the entire range of birth weight, length, and head and chest circumference among all newborns (Fig. 2B). For birth weight and length, the estimates were slightly stronger in the 25th and 50th percentiles compared with the 75th percentile; however, the quantile-specific effect estimates were not significantly different (P > 0.10 for all).

Discussion

This prospective cohort study in rural Bangladesh supported the hypothesis that iodine is essential for adequate fetal growth. A new finding was the positive linear associations between maternal UIC and birth weight and length up to ~1.0 mg/L, which is well above what the WHO considers adequate for pregnant women (median UIC: 0.15–0.25 mg/L) or excessive intake (>0.50 mg/L) (2,22). Iodine seemed to be particularly beneficial for male fetuses, in which birth weight increased by 70 g for a 0.50-mg/L increase in maternal UIC.

The observed fairly modest increase in birth weight over the wide range of maternal UIC is in contrast to the main previous study in this research field (7). That study showed that newborns were 188 g heavier in Spanish women with a UIC of 0.10–0.15 mg/L, compared with those with a UIC < 0.050 mg/L, although a maternal UIC > 0.15 mg/L had no additional effect on birth weight (7). However, this lack of effect may have been due to insufficient statistical power, because only 67 women had such a high UIC. In the present study, 66% of the 1617 women had a UIC > 0.15 mg/L, and the overall median concentration was 0.30 mg/L.

Iodine deficiency is a global concern. In many areas of the world, fortified table salt and supplementation are necessary for adequate iodine status, particularly during pregnancy and lactation. Obviously, the sustainability of such efforts is critical and needs to be monitored. In the ALSPAC study in the United Kingdom, the median UIC is only 0.091 mg/L in pregnant women (n = 958) (6), and the median UIC (0.15 mg/L) among pregnant women in the US NHANES database (n = 326) is at the lower end of the recommended window (23). The latest national Bangladeshi UIC survey, conducted from September 2004 to March 2005, shows a median UIC of 0.14 mg/L among pregnant women in rural areas and 0.29 mg/L in urban areas (24), indicating substantial regional differences. Indeed, a recent study of 1376 pregnant women in the rural northern part of Bangladesh found a very low median UIC of 0.066 mg/L in early pregnancy (25), which is in sharp contrast to the present study in which the 10th percentile was 0.084 mg/L.

The mechanisms behind the positive effect of prenatal iodine status on birth size in boys, but not girls, are not known. To our knowledge, no previous data showed sex-specific effects of iodine on fetal growth. However, the proportion of neonatal blood thyroid-stimulating hormone concentrations above the WHO cutoff for estimated iodine sufficiency is higher for male than for female newborns, especially in those with low birth weight (31,32). Additionally, male fetuses grow more rapidly than do female ones in late gestation, which may increase their susceptibility to malnutrition compared with females (33). Although the effect was mediated partly through the lower risk of preterm birth, we cannot entirely exclude the possibility of

FIGURE 2

Associations of maternal urinary iodine (including women with a urinary iodine concentration < 1.0 mg/L; n = 1457) and birth weight, length, head circumference, and chest circumference after stratification of linear regression analyses by newborn sex (A) and maternal urinary iodine in each quantile (25th, 50th, and 75th) of birth weight, length, and head and chest circumference obtained using quantile regression analyses (including all newborns of women with a urinary iodine concentration < 1.0 mg/L; n = 1457) (B). Estimates with 95% CIs represent the change in newborn size per 0.10 mg/L maternal urinary iodine, adjusted for maternal BMI (gestational week 8), parity, level of formal education (<5 and ≥5 y), season of birth, and gestational age (<37 and ≥37 wk). The quantile regression analyses were additionally adjusted for newborn sex. *Birth weight has been divided by 100 to fit the scale of the figure. Q, quantile; Ul, urinary iodine.
residual confounding by gestational age at birth, although it was not associated with UIC.

The main strengths of the study included the prospective design and the large cohort of pregnant women with a wide range of UIC measured by inductively coupled plasma MS in alkaline solution, which is considered the gold standard for this measurement (34, 35). Also, essentially all of the women studied were non-smokers and none used alcohol, both of which are known to affect birth weight. However, the use of spot urine samples for assessing iodine status on a population basis was questioned (36, 37), because other suggested methods, such as the estimated average requirement cut-point method for UIC or thyroglobulin measurements, may better reflect true iodine intake (37). Nevertheless, a Danish study shows that spot urine samples collected monthly over a 1-year period did not differ significantly in UIC (38). Similarly, repeated UIC measurements in the present cohort indicated a fairly constant increase over the duration of pregnancy in most women (9).

One limitation of the present study was the lack of blood plasma samples for measurement of thyroid hormones. Thyroid hormones, which require iodine for synthesis, may promote the expression and secretion of growth hormones essential for fetal and child growth (39–41). Hypothyroidism, induced by either iodine deficiency or excess intake, was shown to decrease circulating insulin-like growth factor-1 (42).

In conclusion, we found positive associations between maternal iodine status up to ~1.0 mg/L and birth weight, length, and head circumference in male newborns. Iodized table salt and drinking water were likely major sources of iodine, and the variable iodine content in these sources may also explain the marked interindividual variation in UIC. However, evaluation of maternal UIC effects on child thyroid function and child development is warranted before a revision of the maximum UIC is recommended. Nevertheless, the findings support previous conclusions that the advantages of correcting potential iodine deficiency far outweigh the risks of excess exposure (23, 43).

Acknowledgments
M.V. was responsible for this cohort and the research on health effects in relation to toxic exposure and interaction with nutrition and other susceptibility factors and gave considerable input to the manuscript; M.K. initiated this research question, supervised the chemical analyses and the statistical evaluations, and gave considerable input to the manuscript at all stages; M.G. conducted the chemical analyses; F.R. contributed to the chemical analyses and drafting the statistical evaluations and the manuscript; A.R. provided input based on his previous evaluation of the effects of arsenic on birth outcome in the same cohort and reviewed the manuscript; and E.-C.E. contributed to the data acquisition for previous studies and reviewed the manuscript. All authors read and approved the final manuscript.

References


