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IODINE AND PREGNANCY

Mild-to-Moderate Iodine Deficiency in Early Pregnancy Is Associated with Lower Verbal IQ in Children

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SUMMARY

Background

Severe maternal iodine deficiency is known to be associated with low offspring IQ (1). However, the effects of mild-to-moderate maternal iodine deficiency on child neurocognitive outcomes remain poorly understood, and results of cohort studies have been somewhat variable (2-5). The effects of maternal iodine status at different gestational ages on child neurodevelopment have not been examined previously.

Methods

This was an individual-participant meta-analysis (6) performed using data from three European pregnancy cohorts: Generation R in the Netherlands, the INfancia y Medio Ambiente Project (INMA) in Spain, and the Avon Longitudinal Study of Parents and Children (ALSPAC) in the United Kingdom. Mother–child pairs were included if maternal urinary iodine and creatinine levels during pregnancy and child IQ test results were available. Criteria for exclusion were multiple pregnancies, use of fertility treatment, known thyroid disease, or use of thyroid-affecting medications. Urinary iodine and creatinine concentrations were measured in spot urine samples; when more than one measurement was available for a participant, the sample obtained at the earliest time point in gestation was used for analyses. Specimens with urinary iodine concentrations >500 µg/L were excluded from the ALSPAC cohort owing to concerns about iodine contamination from urine test strips. Urinary iodine status was categorized as <150 µg/g of creatinine, 150-499 µg/g, or ≥500 µg/g. Maternal TSH and free T_4 concentrations were measured by different assays in the different cohorts and thus values were log-transformed, and cohort-specific standard deviation scores were calculated in order to make values directly comparable across cohorts. Potential confounders ascertained by questionnaires administered during pregnancy included maternal age, maternal education level, ethnicity, parity, prepregnancy BMI, and smoking during pregnancy. In the Generation R cohort, child nonverbal IQ was measured at a median age of 5.9 years and verbal IQ at a median age of 1.5 years. In the INMA cohort, verbal and nonverbal IQ were assessed at a median age of 4.6 years, and in the ALSPAC cohort at a median age of 8.6 years. Because IQ was assessed using different instruments in each cohort, cohort-specific scores were standardized to a mean (±SD) of 100±15 points. Children with IQs <50 or >150 were excluded.

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Associations of log-transformed urinary iodine-to-creatinine ratios with child IQ were assessed using multivariable linear regression models of the pooled cohort data. Models were adjusted for maternal age, parity, BMI, ethnicity, smoking, gestational age, and child sex (child age at testing and study cohort were not included owing to colinearity with maternal ethnicity). Nonlinearity was assessed by means of quadratic terms and by using ordinary least-squares linear regression models with restricted splines with three knots. Effect modification by gestational age was examined both by introducing an interaction term for gestational age and the urinary iodine-to-creatinine ratio into models and by performing analyses stratified by gestational age at the time of testing. In a second approach to analysis, cohort-specific effect estimates were combined using random-effects meta-analyses, considering the reference group to be women with urinary iodine-to-creatinine ratios of 150 to 500 µg/g of creatinine. Heterogeneity between cohorts was assessed using the I2 statistic and the Cochran Q test. Inverse probability weighting was applied to account for possible differential losses to follow-up. Missing confounder variable data were imputed using chained equations.

Results

The study sample included 6180 mother–child pairs. Median urinary iodine concentrations were 159 µg/L in the Generation R cohort (iodine-sufficient), 128 µg/L in the INMA cohort (mildly iodine-deficient), and 96 µg/L in ALSPAC (moderately iodine-deficient). Urine samples were collected at a median gestational age of 13.1 weeks in Generation R, 13.0 weeks in INMA, and 12.0 weeks in ALSPAC.

There was a positive linear association between the urinary iodine-to-creatinine ratio and nonverbal child IQ in the linear regression models, although this did not achieve statistical significance. There did not appear to be any effect modification by gestational age at testing. Using random-effects meta-analysis the urinary iodine-to-creatinine ratio was not associated with nonverbal IQ. In the linear regression models there was a positive curvilinear association between the urinary iodine-to-creatinine ratio and verbal child IQ (P<0.001). Associations between the urinary iodine-to-creatinine ratio and verbal IQ were seen during the first 12 weeks of pregnancy and between weeks 12 and 14, but not after 14 weeks of gestation. Using random-effects meta-analysis, neither having a urinary iodine-to-creatinine ratio of <150 (−6 IQ points; 95% CI, −1.3 to 0.1) or ≥500 µg/g of creatinine (−0.6 IQ points; 95% CI, −2.6 to 1.4) was associated with verbal IQ. Urinary iodine-to-creatinine ratios were not associated with maternal TSH (P = 0.8) or free T_4 (P = 0.08).

Conclusions

Lower urinary iodine-to-creatinine ratios up through week 14 of gestation were associated with poorer child verbal IQ scores. There were no associations of maternal iodine status with child nonverbal IQ.

COMMENTARY

Strengths of this study include the use of techniques to harmonize laboratory values across cohorts, the ascertainment of a wide range of potentially confounding variables, and the use of methods to try to minimize selection bias from loss to follow-up and from missing data. The study included cohorts with a spectrum of iodine intakes, ranging from moderately deficient through sufficient. The primary study limitations are the use of different instruments for assessment of child IQ and the different timing of child neurocognitive assessments across the cohorts.

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This study adds to the growing body of observational data suggesting that even mild-to-moderate maternal iodine deficiency may have adverse neurodevelopmental consequences for offspring. Randomized clinical trial data are needed to definitively determine whether maternal iodine supplementation in regions in which pregnant women are mildly to moderately iodine-deficient (such as the United States) will improve developmental outcomes. Such studies have been challenging to conduct because in many regions, in light of current recommendations for supplementation, it has been thought to be unethical or unfeasible to include a placebo group.

These data reinforce that timing of iodine supplementation relative to gestational age may be critically important. The first trimester of pregnancy seems to be a particularly crucial time for the thyroid-mediated development of neural pathways related to language ability. The fetal thyroid is not functioning during this period, and the fetus is thus dependent on the maternal thyroid hormone that crosses the placenta. In light of current data, the American Thyroid Association recommends that U.S. women who are planning pregnancy, pregnant, or lactating should ingest a daily supplement containing 150 µg of iodine (7). Ideally, such supplements should be started at least 3 months prior to conception. Future trials evaluating the effectiveness of this strategy should aim to enroll women before conception or at least within the first trimester of pregnancy.

References

1. Zimmermann MB 2009 Iodine deficiency. Endocr Rev **30**:376–408. Epub 2009 May 21.
2. Bath SC, Steer CD, Golding J, Emmett P, Rayman MP 2013 Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). Lancet **382**:331–337. Epub 2013 May 22.
3. Hynes KL, Otahal P, Burgess JR, Oddy WH, Hay I 2017 Reduced educational outcomes persist into adolescence following mild iodine deficiency in utero, despite adequacy in childhood: 15-year follow-up of the Gestational Iodine Cohort Investigating Auditory Processing Speed And Working Memory. Nutrients 9(12). pii: E1354.
4. Abel MH, Caspersen IH, Meltzer HM, Haugen M, Brandlistuen RE, Aase H, Alexander J, Torheim LE, Brantsæter AL 2017 Suboptimal maternal iodine intake is associated with impaired child neurodevelopment at 3 years of age in the Norwegian Mother and Child Cohort Study. J Nutr **147**:1314–1324. Epub 2017 May 17.
5. Rebagliato M, Murcia M, Alvarez-Pedrerol M, Espada M, Fernández-Somoano A, Lertxundi N, Navarrete-Muñoz EM, Forns J, Aranbarri A, Llop S, et al. 2013 Iodine supplementation during pregnancy and infant neuropsychological development. INMA Mother and Child Cohort Study. Am J Epidemiol **177**:944–953. Epub 2013 Apr 1.
6. Levie D, Korevaar TIM, Bath SC, Murcia M, Dineva M, Llop S, Espada M, van Herwaarden AE, de Rijke YB, Ibarluzea JM, et al. 2019 Association of maternal iodine status with child IQ: a meta-analysis of individual-participant data. J Clin Endocrinol Metab. Epub 2019 Mar 28.
7. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, et al. 2017 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid **27**:315–389.