Effect of iodine supplementation in pregnant women on child neurodevelopment: a randomised, double-blind, placebo-controlled trial

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Summary

Background Iodine deficiency during pregnancy might be associated with reduced intelligence quotient (IQ) score in offspring. We assessed the effect of iodine supplementation in mildly iodine-deficient pregnant women on neurodevelopment of their offspring in areas where schoolchildren were iodine sufficient.

Methods In this randomised, placebo-controlled trial, pregnant women in Bangalore, India, and Bangkok, Thailand, were randomly assigned (1:1) to receive 200 µg iodine orally once a day or placebo until delivery. Randomisation was done with a computer-generated sequence and stratified by site. Co-primary outcomes were verbal and performance IQ scores on the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) and the global executive composite score from the Behaviour Rating Inventory of Executive Function-Preschool Version (BRIEF-P) in the children at age 5–6 years. The trial was double-blinded; some unmasking took place at age 2 years for an interim analysis, but participants and nearly all investigators remained masked to group assignment until age 5–6 years. Analysis was by intention to treat using mixed-effects models. This trial is registered with ClinicalTrials.gov, number NCT00791466.

Findings Between Nov 18, 2008, and March 12, 2011, 832 women entered the trial at a mean gestational age of 10·7 weeks (SD 2·7); median urinary iodine concentration was 131 µg/L (IQR 81–213). Mean compliance with supplementation was 87%, assessed by monthly tablet counts. 313 children (iodine group, n=159; placebo group, n=154) were analysed for verbal and performance IQ with WPPSI-III and 315 (iodine group, n=159; placebo group, n=156) for overall executive function with BRIEF-P. Mean WPPSI-III scores for verbal IQ were 89·5 (SD 9·8) in the iodine group and 90·2 (9·8) in the placebo group (difference –0·7, 95% CI –2·9 to 1·5; p=0·77), and for performance IQ were 97·5 (12·5) in the iodine group and 99·1 (13·4) in the placebo group (difference –1·6, –4·5 to 1·3; p=0·44). The mean BRIEF-P global executive composite score was 90·6 (26·2) in the iodine group and 91·5 (27·0) in the placebo group (difference –0·9, –6·8 to 5·0; p=0·74). The frequency of adverse events did not differ between groups during gestation or at delivery: 24 women in the iodine group and 28 in the placebo group reported adverse events (iodine group: abortion, n=20; blighted ovum, and n=2; intrauterine death, n=2; placebo group: abortion, n=22; blighted ovum, n=1; intrauterine death, n=2; early neonatal death, n=1; and neonatal death, n=2).

Interpretation Daily iodine supplementation in mildly iodine-deficient pregnant women had no effect on child neurodevelopment at age 5–6 years.

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Introduction

Iodine is an essential component of thyroid hormones, which are needed for normal fetal growth and development.[1] At week 4 of pregnancy, maternal thyroid hormone is present in utero and promotes neuronal proliferation and migration in the developing brain.[2] Fetal thyroid hormone synthesis begins at about week 20;[2] thereafter, both maternal and fetal thyroid hormones support fetal neurodevelopment.[1,2] To maintain maternal and fetal euthyroidism, iodine requirements during pregnancy increase by about 65%, and WHO recommends an intake of 250 µg per day for pregnant women.[3] In randomised controlled trials in regions of severe endemic goitre, iodine supplementation in pregnancy improved maternal thyroid status and child neurodevelopment.[1]

Although severe iodine deficiency now only rarely occurs in most countries, mild iodine deficiency during pregnancy remains common.[4] WHO recommends measurement of median urinary iodine concentration to assess population-level iodine nutrition during pregnancy; in a population of pregnant women, a median concentration of 150–250 µg/L indicates optimal iodine nutrition whereas 50–150 µg/L suggests mild iodine deficiency.[5] In national studies of pregnant women in Europe, about two-thirds of countries reported mild iodine deficiency based on the median urinary iodine concentration.[4] Pregnant women in the USA are also mildly deficient, with a median urinary iodine concentration of 129 µg/L.[6] Two observational studies

Research in context

Evidence before this study

We searched PubMed with the terms "iodine supplementation" OR "iodine supplements" OR "oral iodine" AND "pregnancy" with no language or date restrictions. The date of our last search was April 24, 2017. Iodine deficiency during pregnancy might be associated with reduced intelligence quotient (IQ) score in offspring. In randomised controlled trials in regions of severe endemic goitre, iodine supplementation in pregnancy improved maternal thyroid status and child neurodevelopment. Two observational studies reported lower IQ and poorer school performance in children born to mildly iodine-deficient mothers than in children of mothers without deficiency, but other studies showed no difference in neurodevelopment between infants of mothers who had mild iodine deficiency and those of mothers who had iodine sufficiency. Controlled trials of iodine supplementation in mildly iodine-deficient pregnant women have shown no clear benefits on maternal or newborn thyroid hormone concentrations. Systematic reviews have concluded that the effects of mild iodine deficiency during pregnancy are uncertain because no placebo-controlled intervention trial has measured child development following maternal iodine supplementation in women with mild iodine deficiency.

Added value of this study

To our knowledge, our study is the first randomised, double-blind, placebo-controlled trial to assess the effects of oral iodine supplementation in mildly iodine-deficient pregnant women on neurodevelopment of their children. We assessed neurocognitive outcomes during infancy and early school age. Although supplementation was safe and increased iodine intake into the sufficient range, we found no significant differences in cognitive developmental scores between children whose mothers were assigned to receive iodine supplementation during pregnancy and children of those assigned to placebo.

Implications of all the available evidence

Our finding that iodine supplementation of mildly iodine-deficient pregnant women had no clear benefits on maternal thyroid function or child neurodevelopment needs to be confirmed in future studies in other populations and other settings. However, our results generally support findings from previous intervention studies suggesting that pregnant women might be able to physiologically adapt to mildly low iodine intakes to maintain fetal euthyroidism, allowing healthy in-utero development. This conclusion is consistent with current WHO recommendations that iodine supplementation is unlikely to harm, but might not be justified in mildly iodine-deficient pregnant women.

reported lower intelligence quotient (IQ) scores and poorer school performance in children born to mildly iodine-deficient mothers than in children of mothers without deficiency;[7,8] another study comparing different doses of iodine supplements in pregnancy showed no effect on neuropsychological development of infants.[9] Controlled trials of iodine supplementation in mildly iodine-deficient pregnant women have shown no clear benefits on maternal or newborn thyroid hormone concentrations.[10] Systematic reviews have concluded that the effects of mild iodine deficiency during pregnancy remain uncertain because no placebo-controlled intervention trial has measured child development.[10,11]

Although they acknowledge the paucity of data regarding benefits, the American Thyroid Association[12] and European Thyroid Association[13] recommend that women take a supplement containing 150 µg iodine daily during pregnancy. By contrast, WHO does not recommend maternal iodine supplements in countries with iodised salt programmes,[14] concluding that if women are iodine sufficient before they enter pregnancy, they can cover their requirements by increasing fractional clearance of plasma iodide and drawing from thyroidal iodine stores. Of concern, observational studies have linked excessive maternal iodine intake with mild maternal hypothyroidism,[15] and maternal iodine supplementation with impaired infant development.[9] Therefore, we aimed to assess the safety and efficacy of iodine supplementation in mildly iodine-deficient pregnant women on child neurodevelopment. Our hypothesis was that iodine supplementation of this group would be safe, but would have no significant benefits on child development.

Methods

Study design and participants

This randomised, placebo-controlled, double-blind trial was done at Ramathibodi Hospital of Mahidol University in Bangkok, Thailand, and St Martha's Hospital in Bangalore, Karnataka, India. These hospitals were chosen because they had large, well-run antenatal clinics and served mainly middle-income families. We chose only one hospital at each site to simplify logistics and follow-up. Although, in 2017, Thailand and India have effective salt iodisation programmes and women of reproductive age are iodine sufficient at the national level,[16] at the time of our intervention, no data were available for iodine status in women of reproductive age, and household coverage with adequately iodised salt was only about 35% in Karnataka and 60% in Thailand, but school-aged children (aged 6–12 years) were iodine sufficient on the basis of their median urinary iodine concentration.[17,18]