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Effect of iodine supplementation in pregnancy on child development and other clinical outcomes: a systematic review of randomized controlled trials[1–4]

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ABSTRACT

Background: Routine iodine supplementation during pregnancy is recommended by leading health authorities worldwide, even in countries where the iodine status of the population is sufficient.

Objectives: We evaluated the efficacy and safety of iodine supplementation during pregnancy or the periconceptional period on the development and growth of children. Secondary outcomes included pregnancy outcome and thyroid function.

Design: A systematic review of randomized controlled trials (RCTs) was conducted. PUBMED, MEDLINE, EMBASE, CINAHL, PsycINFO, and Cochrane Central Register of Controlled Trials databases were searched to identify relevant RCTs.

Results: Fourteen publications that involved 8 trials met the inclusion criteria. Only 2 included trials reported the growth and development of children and clinical outcomes. Iodine supplementation during pregnancy or the periconceptional period in regions of severe iodine deficiency reduced risk of cretinism, but there were no improvements in childhood intelligence, gross development, growth, or pregnancy outcomes, although there was an improvement in some motor functions. None of the remaining 6 RCTs conducted in regions of mild to moderate iodine deficiency reported childhood development or growth or pregnancy outcomes. Effects of iodine supplementation on the thyroid function of mothers and their children were inconsistent.

Conclusions: In this review, we highlight a lack of quality evidence of the effect of prenatal or periconceptional iodine supplementation on growth and cognitive function of children. Although contemporary RCTs of iodine supplementation with outcomes addressing childhood development are indicated, conduct of such RCTs may not be feasible in populations where iodine supplementation in pregnancy is widely practiced. *Am J Clin Nutr* doi: 10.3945/ajcn.113.065854.

INTRODUCTION

Iodine is essential for the production of thyroid hormones, which, in turn, are important for normal growth and development. Severe iodine deficiency in pregnancy causes cretinism and irreversible brain damage in offspring (1). The epidemiology of iodine deficiency has changed after the implementation of universal salt iodization programs in countries where iodine deficiency was identified as a public health problem, and severe iodine deficiency is now rare (2). However, mild to moderate iodine deficiency continues to be cited as a problem, and reports have emerged from a number of industrialized countries (3, 4). Leading health authorities worldwide have recommended routine iodine supplementation during pregnancy because of the concern that mild to moderate iodine deficiency in pregnancy may also impair the cognitive ability of offspring (5–8).

Although reviews on iodine nutrition and the development of children exist, most of the reviews included results of observational studies (9–12), which could not determine the causal relation between iodine status and neurodevelopment. We have been unable to find any systematic reviews of randomized controlled trials (RCTs)[5] that assessed cause-and-effect relations and were performed by using comprehensive search strategies, well-documented inclusion or exclusion criteria, and assessments of risk of bias. In this systematic review, we aimed to determine the efficacy and safety of iodine supplementation during pregnancy or the periconceptional period, reported according to contemporary guidelines (13, 14).

METHODS

Search strategy and selection criteria

We searched the Cochrane Central Register of Controlled Trials (http://onlinelibrary.wiley.com/cochranelibrary/search?searchRow.searchOptions.searchProducts=clinicalTrialsDoi), EMBASE (http://www.embase.com/), MEDLINE (http://www.nlm.nih.gov/medlineplus/), Cumulative Index to Nursing and Allied Health Literature (http://www.ebscohost.com/academic/cinahl-plus-with-full-text), PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), and

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[5] Abbreviations used: IQ, intelligence quotient; RCT, randomized controlled trial; TBG, thyroxine-binding globulin; TSH, thyroid-stimulating hormone or thyrotropin.

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PsycINFO (http://www.apa.org/pubs/databases/psycinfo/index.aspx) databases from inception through December 2012 for relevant articles according to the search strategy (*see* Supplement Appendix 1 under "Supplemental data" in the online issue) specified in the predefined protocol. All RCTs (including those with a quasirandom design) that compared the effect of iodine supplementation with a parallel control group who received no iodine supplementation (or placebo) during pregnancy or the preconceptional period on clinical or biochemical outcomes were eligible for inclusion in the review. Pregnant women or those of childbearing age regardless of iodine status or gestation at trial entry were included. Trials were eligible for inclusion in which women received any form of iodine supplementation, with or without other nutrients, in which the only difference between the treatment and comparison group was the presence or absence of iodine. The primary outcome was the cognitive development of children. Secondary outcomes included pregnancy and birth outcomes, childhood growth and mortality, iodine status, and thyroid function of mothers and infants. The search was restricted to human studies without language restrictions. Reference lists of relevant retrieved publications identified by the search and recent review articles were also checked for additional studies. Titles and abstracts of all articles retrieved by the search were used to assess eligibility by 2 independent reviewers. If there was insufficient information to warrant the exclusion of an article from the abstract, the full text of the article was retrieved to determine eligibility. Any discrepancies were resolved by consensus through discussion or by a third reviewer.

Quality assessment, data extraction, and analysis

Two reviewers (SJZ and AJA) independently assessed risk of bias of each included study by using the Cochrane Risk of Bias tool and extracted all study data by using a standardized data extraction form (14). Discrepancies were resolved by consensus through discussion or by a third reviewer. Although a statistical analysis was originally planned, it was not possible to conduct a meta-analysis because of the scarcity of essential data.

RESULTS

The search returned a total of 138 publications. An additional 23 potentially relevant publications were identified by checking references of included studies and relevant review articles. After removing duplicates, 109 publications remained. Of these articles, 95 publications were excluded because the studies did not meet the predefined inclusion criteria (*see* Supplement Appendix 1 under "Supplemental data" in the online issue). A total of 14 publications involving 8 trials were included in the review (**Figure 1**) (15–28).

Participants, setting, and intervention

Two trials were conducted in rural settings in areas of severe iodine deficiency as indicated by the high incidence of endemic goiter and cretinism (17, 21). Both trials were quasi-RCTs conducted >40 y ago. In the landmark trial conducted in Papua New Guinea in 1966, 27 villages with a combined population of 16,500 participated in the trial (21). Alternate families received a single injection of either iodized oil (containing 1600 mg iodine) or a placebo. The other study was conducted in 3 villages in Peru, and 3183 participants (both female and male subjects) were injected with either iodized oil [containing 960 mg iodine (or 96 mg iodine if a nodular goiter was present)] or poppy seed oil (without iodine) by alternate allocation (17). Children born after the commencement of the intervention program and their mothers were assessed. The design and key findings of these 2 studies are summarized in **Table 1**.

The remaining 6 trials were conducted in pregnant women from regions of mild to moderate iodine deficiency on the basis of

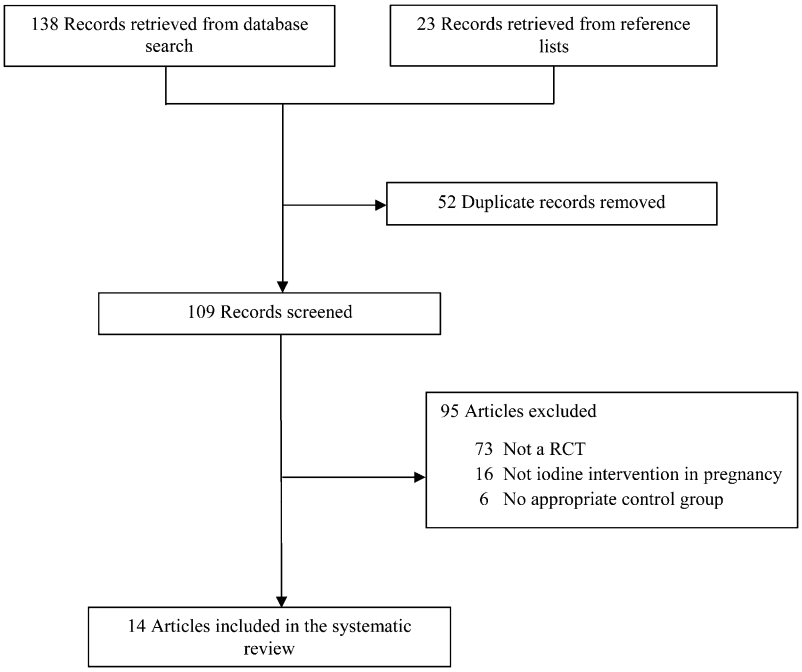

FIGURE 1. Flowchart of literature search and eligibility of studies in the systematic review. RCT, randomized controlled trial.

TABLE 1
Clinical outcomes (other than biomarkers) of the included controlled trials in regions of severe iodine deficiency[1]

First author, year of publication (reference)	Setting and participants	Intervention	Result
Kevany, 1969 (17)[2] Pretell, 1972 (26) Pretell, 1974 (24) Pretell, 1994 (25)	Quasi-RCT (alternate families) in Peru: 3 central Sierra villages, 1966 n = 3183 (747 were women of childbearing age) (24) UIE of population: 17 μg/24 h[2]	Intervention (n = 1992) (24): Iodine A: 2 mL iodized oil containing 960 mg iodine if >6 y old, no nodular goiter Iodine B: 0.2 mL iodized oil containing 96 mg iodine if nodular goiter present Control (n = 1191) (24): poppy seed oil without iodine Duration: single injection in 1966, followed by a reinjection 3 y later when a new group of participants were injected for the first time	Development of children at 5-y follow-up *1*) Gross development: no diff (~70% of children tested) (26)[3] *2*) IQ: no diff (n = 35 iodine; n = 46 control)[3] *3*) IQ (subgroup analysis): iodine (n = 28) > control (n = 44) (P = 0.002) (25)[4] *4*) Psychological retardation (subgroup analysis): iodine (n = 28) < control (n = 44) (P = 0.0001)[4] *5*) Mental deficiency: iodine (n = 35) 17% compared with control (n = 46) 33% (P = NR)[3] *6*) Language deficiency: iodine (n = 35) 46% compared with control (n = 46) 58% (P = NR)[3] *7*) Language deficiency (subgroup analysis): iodine (n = 28) ~39% compared with control (n = 44) ~57% (P = NR)[4] *8*) Hearing deficiency: iodine (n = 35) 0% compared with control (n = 46) 11% (P = NR)[3] *9*) Hearing deficiency (subgroup analysis): iodine (n = 28) 0% compared with control (n = 41) ~10% (P = NR)[4] *10*) Cretinism: no obvious cretins detected in the series[3] *11*) EEG 2–4 y: iodine (n = 9 of 9) normal compared with control (n = 11 of 12) normal (P = NR)[3]

(Continued)

TABLE 1 (*Continued*)

First author, year of publication (reference)	Setting and participants	Intervention	Result
			12) EEG 2–4 y (subgroup analysis): iodine (n = 7 of 7) normal compared with control (n = 10 of 11) normal (P = NR)[4]
			Growth of children at 5-y follow-up
			1) Skinfold thicknesses and upper arm circumferences: no diff (n = NR)[3,4]
			2) Growth rate of children: slightly higher iodine compared with control (n = NR, P = NR)[3]
			3) Postnatal bone maturation birth to 5 y of age: no diff (n = NR)[3]
			Pregnancy outcome
			1) Births registered at 5 y poststudy commencement: 456 (44% in control (P = NR)[3,4]
			2) Intrauterine hypothyroidism (ossification from birth X-ray): no diff (0%)[3]
			3) Goiter rate of newborns: no diff (0%)[3]
			4) Birth anthropometric measures (placental weight, body weight, length, head circumference): no diff (n = NR)[3,4]
			5) APGAR scores at birth: no diff (n = NR)[3]
			Other clinical outcome
			Mortality rate of children ≤2 y old: no diff (n = NR)[3]
Pharoah, 1971 (21)[5] Connolly, 1979 (15) Pharoah, 1987 (22) Pharoah, 1991 (23)	Quasi-RCT (alternate individuals) in Papua New Guinea: 27 villages in Jimi river valley, 1966 n= ∼16,500	Intervention: iodized oil (4 mL, if aged >12 y) containing ∼1600 mg iodine Control: saline solution	Development of children
			1) Cretinism at 4-y follow-up: iodine (n = 7 of 412 examined, 6 conceived before intervention) compared with control (n = 26 of 406 examined, 5 conceived before intervention)[5]
		Duration: single IM injection in 1966	*2*) Definite cretins at 10–16-y follow-up: iodine (n = 3 of 274, all conceived before intervention) compared with control (n = 16 of 248, 2 conceived before injection) ($P < 0.001$)[6]
			3) Possible cretins at 10–16-y follow-up: iodine (n = 3 of 274, 1 conceived before intervention) compared with control (n = 11 of 248, 2 conceived before injection) ($P < 0.001$)[6]

(Continued)

TABLE 1 (*Continued*)

First author, year of publication (reference)	Setting and participants	Intervention	Result
			4) Developmental score <10th percentile at 10–16-y follow-up: iodine 13 of 235 compared with control 17 of 192 ($P < 0.001$)[6] *5*) Grip strength: no diff at ~11 y of age (n = 115 iodine; n = 79 control)[7] *6*) Grip strength (subgroup analysis): no diff at ~11 y of age (n = 12 iodine; n = 17 control); no diff at ~15 y of age (n = 13 iodine; n = 15 control)[8] *7*) Speed of movement: no diff at ~11 y of age (n = 115 iodine; n = 79 control)[7] *8*) Speed of movement (subgroup analysis): no diff at ~11 y of age (n = 12 iodine; n = 18 control); 15 y (NR)[8] *9*) Unimanual accuracy: screws: no diff at ~11 y of age (n = 115 iodine; n = 79 control)[7] Pegboard: iodine > control at ~11 y of age (n = 115 iodine; n = 79 control ($P < 0.05$) *10*) Unimanual accuracy (subgroup analysis): screws: no diff at ~11 y of age (n = 12 iodine; n = 17 control)[8] 15 y of age (NR)[8] Pegboard: no diff at ~11 y of age (n = 12 iodine; n = 18 control); no diff at ~15 y of age (n = 13 iodine; n = 16 control)[8] *11*) Bimanual accuracy: iodine > control (n = 115 iodine; n = 79 control ($P < 0.01$) at ~11 y of age[7] *12*) Bimanual accuracy (subgroup analysis): no diff at ~11 y of age (n = 11 iodine; n = 17 control); no diff at ~15 y of age (n = 13 iodine; n = 16 control)[8] *13*) Motor impairment: iodine better than control in 5 of 6 age groups (P-value, no. of children for each age group not reported)[7] *14*) Cognitive function: no diff at ~15 y of age (n = 13 iodine; n = 15 control)[8] Growth of children Height: no diff at ~15 y of age (n = 13 iodine; n = 16 control)[8]

(Continued)

TABLE 1 (*Continued*)

First author, year of publication (reference)	Setting and participants	Intervention	Result
			Pregnancy outcome Births registered 4 y postintervention: 498 births in iodine group compared with 534 births in control group[5] Other clinical outcome *1*) Deaths in children registered 4 y after maternal intervention: $n = 66$ in iodine compared with $n = 97$ in control[5] *2*) Goiter rate of adult women: no diff[6] *3*) Goiter rate of children: no diff[6] *4*) 15-y cumulative survival rate in children: iodine > control ($P = 0.002$)[6]

[1] APGAR, Appearance, Pulse, Grimace, Activity, Respiration; diff, difference; EEG, electroencephalogram; IM, intramuscular; IQ, intelligence quotient; NR, not reported; RCT, randomized controlled trial; UIE, urinary iodine excretion.

[2] Only data from the Peru RCT are presented in the table.

[3] Pretell et al, 1972 (26). At the 5-y follow-up, the IQ of children was assessed in one village only; 49 control compared with 43 iodine-treated subjects were assessed. Children conceived before the intervention ($n = 8$ of 43 iodine compared with 3 of 49 control) were excluded from the analysis of IQ and developmental deficiency. Fifteen children from each group were assessed for an EEG (children conceived before the intervention were excluded).

[4] Pretell and Caceres, 1994 (25). Subgroup analysis of the 5-y follow-up; 89 children ($n = 40$ iodine; $n = 49$ control) from one of the villages were assessed. For the control group, only children whose mothers had UIE or thyroxine that was consistent with iodine deficiency were included ($n = 44$). For the iodine group, only children whose mothers had UIE or thyroxine that was considered normal were included ($n = 28$).

[5] Pharoah et al, 1971 (21). Only 16 of 27 villages were followed up.

[6] Pharoah and Connolly, 1987 (22). Follow-up of children (aged 10–16 y) born between 1966 and 1972 and mothers from 5 of the original villages that showed the greatest incidence of cretinism ($n = 274$ iodine; $n = 248$ control). Children conceived before trial entry or children classified as definite or possible cretins were excluded in the statistical analysis of the developmental score <10th percentile.

[7] Connolly et al, 1979 (15). Eleven-year follow-up of children (various ages; $n = 208$ tested) in Pharoah et al, 1971 (21) from 5 of the original villages that showed the greatest incidence of cretinism. Cretin children were excluded ($n = 1$ iodine; $n = 13$ control). For motor impairment, only $n = 3$ tested for the 9-y-old age group.

[8] Pharoah and Connolly, 1991 (23). Eleven-year (in 1978) and 15-y (in 1982) follow-up of children in Pharoah et al 1971 (21) from 5 of the original villages that showed the greatest incidence of cretinism. Subgroup analysis of children born ≤40 wk of mother receiving the intervention [ie, these children were conceived before the intervention ($n = 11$–13 iodine; $n = 15$–18 control)].

the median urinary iodine concentration. Five trials were conducted in hospital or clinic settings in Europe, and the other trial was conducted in rural Chile (16, 18–20, 27, 28). Women were randomly assigned to receive either iodine or placebo supplements daily from trial entry (from 9 to 32 wk of gestation) to delivery or into the postpartum period (16, 18–20, 27, 28). The form of supplementation included iodized salt, potassium iodide drops, or potassium iodide tablets, but the form was unclear in one trial (16, 18–20, 27, 28). The dose of iodine ranged from 100 to 300 μg/d. Sample sizes were small and ranged from 35 to 250 participants. Only 3 trials had >100 participants (16, 18, 28). Designs and findings of the 6 trials are summarized in **Tables 2** and **3**. No RCTs from regions of iodine sufficiency were identified.

Quality of studies

None of the trials reported adequate random-sequence generation or adequate allocation concealment (**Table 4**). Inadequate sequence-generation procedures included the allocation by day of the week, alternate allocation, or not treating every fourth person to form the control group (17, 18, 21, 28). The majority of trials did not provide sufficient detail to assess the potential bias on the blinding of participants and personnel, and only 2 trials were judged to be at low risk (16, 19). Risk of bias from incomplete reporting of outcome data was low in only one trial, and in general, numbers of participants treated and followed-up were not clearly reported (27). One trial was assessed as being at high risk of other bias because of the follow-up processes, which were focused on 5–16 of the original 27 villages, with the focus on villages with the highest prevalence of cretinism (21).

Growth and development of children

Studies in regions of severe iodine deficiency

In the Peru trial, the gross development of newborns was assessed by using the Gesell test in ~70% of newborns, and there was no difference between iodine and placebo groups (17, 26). In one of the 3 villages, there were no differences in mean test scores between iodine and placebo groups of children aged between 3 mo and 4 y who were assessed by using the Brunet-Lezine test (<2 y) and the Stanford-Binet test (>2 y) (Table 1) (26). In a subgroup analysis reported subsequently, children whose mothers had urinary iodine excretion or thyroxine consistent with iodine deficiency in the placebo group (n = 44 of 49) and those with concentrations considered normal in the iodine group (n = 28 of 43) were analyzed (25). In iodine compared with placebo groups, the mean intelligence quotient (IQ) score of children was higher (85.6 ± 13.9 compared with 74.4 ± 14.8, respectively; P = 0.002), and psychological age retardation was lower (15.5 ± 11.6% compared with 26.6 ± 14.1%, respectively; $P < 0.0001$). No differences between groups were reported for the growth rate, skinfold thicknesses, and postnatal bone maturation up to 5 y of age between the 2 groups (Table 1) (25, 26).

In the Papua New Guinea trial, developmental outcomes of children were assessed up to 15 y postintervention (15, 21–23). The incidence of cretinism in the 27 villages originally randomly assigned was 2% (7 of 412 subjects) in the iodine group compared with 6% (26 of 406 subjects) in the placebo group, although no statistical comparison was reported (21). In the subsequent follow-up of the 5 selected villages with the highest incidence of cretinism, incidences of definite cretins and possible cretins were significantly lower in the iodine compared placebo groups (Table 1) (22). The motor functioning of children was assessed by using various tasks, and although there were no differences in grip strength or the speed of movement between groups, children in the iodine group performed better in 2 of 3 speed and accuracy tasks (15). A subgroup analysis of children born ≤40 wk of intervention reported no differences in the performance of any of the motor-functioning tasks (23). There was also no difference in performance on the cognitive-function task between iodine and placebo groups (Table 1), although the number of children included in the subgroup analyses was small (11–13 children in the iodine group and 15–18 children in the placebo group) (23). After the exclusion of children conceived before trial entry and cretins, fewer children in the iodine group had a developmental score <10th percentile compared with that of children in the placebo group (Table 1) (22). The only growth data reported were heights of children at the 15-y follow-up, with no difference between the 2 groups, although only 29 children (13 children in the iodine group and 16 children in the placebo group) were included (Table 1).

Studies in regions of mild to moderate iodine deficiency

None of the 6 trials reported outcomes related to the growth or development of children.

Pregnancy and other clinical outcomes

Studies in regions of severe iodine deficiency

In the Peru trial, initial numbers of births registered were 58 births in the iodine group and 34 births in the placebo group (17). Five years after the intervention, births to iodine-supplemented women of childbearing age were 254/390 (number of births/total number of fertile-aged women) (65%) compared with 202/402 (number of births/total number of fertile-aged women) (50%) in the placebo group (26). In the Papua New Guinea study, there were 498 births in the iodine group compared with 534 births in the placebo group 4 y after the intervention (21). No statistical comparisons were reported in either study. Birth weight, length, head circumference, placental weight, or Appearance, Pulse, Grimace, Activity, Respiration scores at birth were reported only in the Peru trial and did not differ between iodine and the placebo groups (17, 25, 26). Neither trial reported the gestational age at birth, incidence of miscarriage, or preterm birth.

Child mortality ≤2 y of intervention was ~11–12% in the Peru study with no difference between iodine and placebo groups (17). In the Papua New Guinea study 4 y after the commencement of the trial, 66/498 (number of deaths/total number of births) deaths were reported in the iodine group, and 97/534 (number of deaths/total number of births) deaths were reported in the placebo group (21). Fifteen-year cumulative survival rates in a subgroup of children born in 5 of 27 villages (with the highest goiter rate) were significantly higher in the iodine group than placebo group (~85% compared with ~70% survival rates estimated from Figure 1) (22). There were no predefined safety measures or adverse effects in either of the included trials. One case of global developmental delay in the

TABLE 2
Clinical outcomes (other than biomarkers) of included controlled trials in regions of mild to moderate iodine deficiency[1]

First author, year of publication (reference)	Setting and participants	Intervention	Result
Glinoer, 1995 (16)	Belgium: prenatal clinic (first visit), Saint-Pierre University Hospital, Brussels *n* enrolled: 180, divided into 3 equal groups Eligibility: pregnancies (<16 wk GA) with excessive thyroid stimulation[2] GA at trial entry: mean of 14.4 wk Overall MUIC before intervention 36 μg/L	Intervention (*n* = NR) Group B: 131 μg KI/d (100 μg iodine/d) Group C: 131 μg KI + 100 μg L-T_4/d (161 μg iodine/d) Control (*n* = NR): group A, placebo (details NR) Duration: trial entry to delivery	Development of children: NR Growth of children: NR Pregnancy outcome: NR Other clinical outcome: NR
Liesenkötter, 1996 (18)	Germany: Pregnancy Care Unit, Benjamin Franklin Hospital, Free University, Berlin *n* enrolled: 108 [7 subjects had positive TPO-Ab (6 control; 1 iodine) at the beginning of pregnancy; 14 subjects had a history of goiter (7 subjects had an evident goiter at first presentation)] GA at trial entry: mean of 11.2 wk Mild ID (baseline MUIC of participants: 53.2 μg iodine/g creatinine or 6.4 μg/dL)	Intervention (*n* = 38): iodine: 300 μg KI/d Control (*n* = 70): no iodine supplements (whether received placebo NR) Duration: trial entry to 2–21 d PP	Development of children: NR Growth of children: NR Pregnancy outcome: NR Other clinical outcome: NR
Nøhr, 2000 (19)	Denmark: Aalborg Hospital (routine antenatal), Aalborg *n* enrolled: 72, all TPO–Ab positive (≥100 U/mL) but none had history of thyroid disease or clinical symptoms of thyroid dysfunction GA at trial entry: 11 wk Mild-moderate ID area (author assigned)	Intervention Iodine A (*n* = 22): vitamin and mineral tablet containing iodine 150 μg/d (in pregnancy and up to 9 mo PP) Iodine B (*n* = 24): vitamin and mineral tablet containing iodine 150 μg/d (iodine in pregnancy only, placebo in PP) Control (*n* = 26): placebo of vitamin and mineral tablet without iodine Duration: trial entry to delivery or 9 mo PP	Development of children: NR Growth of children: NR Pregnancy outcome: NR Other clinical outcome: NR
Pedersen, 1993 (20)	Denmark: outpatient clinic (routine antenatal), Randers *n* enrolled: 74 (20 dropped out after the first visit, 54 were included in the analysis). No subjects had a history of thyroid disease or were taking iodine supplements/medication that affected thyroid function GA at trial entry: 17–18 wk Area of mild ID (MUIE of the area ∼50 μg/d)	Intervention (*n* = 28): 10 drops KI solution/d containing iodine 200 μg Control (*n* = 26): details NR Duration: trial entry to 12 mo PP	Development of children: NR Growth of children: NR Pregnancy outcome: NR Other clinical outcome: NR
Romano, 1991 (27)	Italy: Obstetrics and Gynecology Department, University of L'Aquila, L'Aquila *n* enrolled: 35 (excluded if history of thyroid disease) GA at trial entry: TM 1 Moderate ID [MUIE (means ± SDs) at first visit: control, 30.5 ± 42.0 μg/24 h; iodine, 37.0 ± 36.0 μg/24 h; *n* = 18 control, *n* = 17 iodine]	Intervention (*n* = 17): iodized salt containing iodine 20 mg/kg salt (∼120–180 μg iodine/d) Control (*n* = 18): detail NR Duration: trial entry to delivery	Development of children: NR Growth of children: NR Pregnancy outcome: NR Other clinical outcome: NR

(Continued)

TABLE 2 (*Continued*)

First author, year of publication (reference)	Setting and participants	Intervention	Result
Silva, 1981 (28)	Chile: prenatal out-patient clinics (serving suburban and rural areas), Eastern Greater Santiago *n* enrolled: 250 GA at trial entry: varied, minimum 9 wk Mild ID [baseline MUIC (means ± SDs): control, 54 ± 36 μg iodine/g creatinine; iodine, 53 ± 33 μg iodine/g creatinine; *n* = 10 control, *n* = 36 iodine]; 50% of subjects had a UIC ≤50 μg iodine/g creatinine	Intervention (*n* = 160): KI solution (10 drops) daily containing iodine ~300 μg/d Control (*n* = 90): no placebo Duration: trial entry to delivery	Development of children: NR Growth of children: NR Pregnancy outcome: NR Other clinical outcome: NR

[1] GA, gestational age; ID, iodine deficiency; KI, potassium iodide; L-T_4, levothyroxine; MUIC, median urinary iodine concentration; MUIE, median urinary iodine excretion; NR, not reported; PP, postpartum; TM, trimester; TPO-Ab, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone or thyrotropin; UIC, urinary iodine concentration.

[2] Excessive thyroid stimulation characterized by serum thyroglobulin abnormally elevated (>20 μg/L) and free thyroxine index ≤1.23 and/or molar triiodothyronine:thyroxine ratio ≥25×10^{-3}, normal serum TSH (0.2–4.0 mU/L), no detectable TPO-Ab or thyroglobulin antibodies, and no history of thyroid disease.

iodine group and one case of Down syndrome in each of the iodine and placebo groups were noted in the Peru trial (26).

Studies in regions of mild to moderate iodine deficiency

None of the 6 trials reported pregnancy or other clinical outcomes.

Iodine status and thyroid function

Studies in regions of severe iodine deficiency

Breast-milk iodine concentrations and urinary iodine excretions in mothers and infants were assessed in the Peru trial and were higher in the iodine-supplemented group than placebo group (*see* Supplement Table 2 under "Supplemental data" in the online issue) (17). Both trials reported higher maternal thyroxine in the iodine-supplemented group and no differences in maternal thyroxine-binding globulin (TBG) between groups. Infant thyroxine, maternal or infant thyroid-stimulating hormone or thyrotropin (TSH), and triiodothyronine were not different between groups in the only trial that reported these outcomes (17). Neither of the studies reported thyroglobulin concentrations or autoimmune thyroid disease or thyroid dysfunction. Although the thyroid volume was not reported, goiter rates did not differ between groups, and no congenital goiter was detected in infants (*see* Supplement Table 2 under "Supplemental data" in the online issue) (22, 26).

Studies in regions of mild to moderate iodine deficiency

Similar to the results from regions of severe iodine deficiency, iodine supplementation led to increases in both maternal (all 6 trials) and infant (3 trials) urinary iodine excretions as well as iodine concentrations in breast milk (2 trials) when assessed (*see* Supplement Table 2 under "Supplemental data" in the online issue) (16, 18–20, 27, 28). No obvious dose-response relation was seen. The effects of iodine supplementation on changes in thyroid hormone concentrations in mothers and infants were not consistent (Table 3; *see* Supplement Table 2 under "Supplemental data" in the online issue). When assessed in mothers, higher thyroxine concentrations were reported in 1 of 5 trials, lower TSH was reported in 1 of 6 trials, and lower thyroglobulin concentrations were reported in 2 of 4 trials in the iodine-supplemented group compared with control group (16, 20, 28). In infants of iodine-supplemented mothers, significant reductions in cord blood thyroglobulin were observed in 2 of 4 trials, and cord blood thyroxine was increased in 1 of 3 trials (16, 20, 28). There were no reports of significant changes in maternal triiodothyronine/free triiodothyronine or TBG, infant free thyroxine, triiodothyronine, TBG, or TSH between supplemented and control groups (Table 3; *see* Supplement Table 2 under "Supplemental data" in the online issue).

Markers of autoimmune thyroid diseases, including thyroid peroxidase antibodies and thyroglobulin antibodies, were not different between groups in the 3 trials that reported this outcome, and 2 of 3 trials also reported the incidence of postpartum thyroid disease (18–20). Four women had thyroid peroxidase antibodies at trial entry in one of the trials; no abnormality in thyroid function was observed in the 2 women in the control group, whereas the 2 women in the iodine-supplemented group developed hyperthyroidism or subclinical hypothyroidism after

TABLE 3
Summary of thyroid-function changes after iodine supplementation during pregnancy[1]

First author, year of publication (reference)	TSH	Tg	T_3	T_4	TBG
Studies in regions of severe iodine deficiency					
Kevany, 1969 (17)	Maternal: no diff during pregnancy, at delivery, or PP (24) Infant: no diff (24)	Maternal: NR Infant: NR	Maternal: no diff during pregnancy (24) Infant: only 2 iodine and 3 control observations reported (24)	Maternal: T_4: iodine > control in last 5 mo of pregnancy (P = NR) and at delivery ($P < 0.001$) (24) FT_4: in pregnancy (timing unclear) iodine > control ($P = 0.001$) (24) Dialyzable fraction T_4: in pregnancy (timing unclear) iodine > control ($P = 0.001$) (24) Infant: no diff (24)	Maternal: no diff endogenous distribution or T_4-binding capacity (24) Infant: NR
Pharoah, 1971 (21)	Maternal: NR Infant: NR	Maternal: NR Infant: NR	Maternal: NR Infant: NR	Maternal: 4–5 y after injection, during pregnancy, TT_4 iodine > control (P = NR) (22) Infant: NR	Maternal: 4–5 y after injection, during pregnancy, no diff (22) Infant: NR
Studies in regions of mild to moderate iodine deficiency					
Glinoer, 1995 (16)	Maternal: group B iodine < control TM 3 ($P < 0.01$) and delivery ($P < 0.001$) Infant: no diff group B iodine compared with control	Maternal: group B iodine < control TM 2, TM 3 and delivery ($P < 0.001$) Infant: group B iodine < control ($P = 0.0001$)	Maternal: no diff group B iodine compared with control during pregnancy Infant: no diff group B iodine compared with control	Maternal: no diff TT_4 or FT_4 group B iodine compared with control during pregnancy Infant: no diff TT_4 or FT_4 group B iodine compared with control	Maternal: cited no diff group B iodine compared with control (data not presented) Infant: no diff TBG or TBG saturation by T_4 group B iodine compared with control
Liesenkötter, 1996 (18)	Maternal: no diff PP Infant: NR	Maternal: no diff PP Infant: NR	Maternal: no diff PP Infant: NR	Maternal: no diff PP Infant: NR	Maternal: no diff PP Infant: NR
Nøhr, 2000 (19)	Maternal: no diff 35 wk pregnancy Infant: NR	Maternal: no diff 35 wk pregnancy Infant: NR	Maternal: no diff TT_3 or FT_3, 35 wk pregnancy Infant: NR	Maternal: no diff TT_4 or FT_4, 35 wk pregnancy Infant: NR	Maternal: NR Infant: NR
Pedersen, 1993 (20)	Maternal: relative changes reported within groups, changes between groups unclear Infant: no diff	Maternal: Tg values from the 2 groups were significantly different at all periods (P = NR) Infant: iodine < control ($P = 0.0005$)	Maternal: no diff during pregnancy Infant: no diff	Maternal: no diff T_4 or FT_4, during pregnancy Infant: no diff T_4 or FT_4	Maternal: NR Infant: NR
Romano, 1991 (27)	Maternal: cited no diff at any TM (data not presented) Infant: NR	Maternal: NR Infant: NR	Maternal: NR Infant: NR	Maternal: NR Infant: NR	Maternal: NR Infant: NR

(Continued)

TABLE 3 (*Continued*)

First author, year of publication (reference)	TSH	Tg	T_3	T_4	TBG
Silva, 1981 (28)	Maternal: no diff at delivery Infant: no diff	Maternal: NR Infant: NR	Maternal: no diff T_3 or rT_3 at delivery Infant: no diff T_3; rT3 iodine > control ($P < 0.005$)	Maternal: T_4 iodine > control at delivery ($P < 0.001$) Infant: T_4 iodine > control ($P < 0.001$)	Maternal: NR Infant: NR
Summary of the number of studies reporting a significant effect of iodine intervention[2]					
Maternal	↓ 1/7	↓ 2/4	0/6	↑ 3/7	0/4
Infant (cord)	0/4	↓ 2/2	↑ 1/1 rT_3	↑ 1/4	0/1

[1] diff, no difference; FT_3, free triiodothyronine; FT_4, free thyroxine; NR, not reported; PP, postpartum; rT_3, reverse triiodothyronine; T_3, triiodothyronine; T_4, thyroxine; TBG, thyroxine-binding globulin; Tg, thyroglobulin; TM, trimester; TSH, thyroid-stimulating hormone or thyrotropin; TT_3, total triiodothyronine; TT_4, total thyroxine; ↓, decreased; ↑, increased.

[2] Data are presented as follows: total number of studies reporting this outcome/number of studies reporting significant effects of iodine supplementation.

birth that persisted at the 12-mo follow-up (20). There was no difference in the incidence of postpartum thyroid dysfunction between groups in the other trial (19).

Women in the iodine-supplemented group compared with women in the control group had lower thyroid volumes in 1 (27) of 2 trials (18, 27) that reported this outcome (*see* Supplement Table 2 under "Supplemental data" in the online issue). Two other trials showed that supplementation reduced pregnancy increases in maternal thyroid volume; however, results were analyzed as percentage changes within groups and not based on the intention-to-treat principle (16, 20). Children of supplemented mothers had lower thyroid volumes than did children of nonsupplemented mothers in the 2 trials that reported this outcome (16, 18).

DISCUSSION

Our systematic review was designed to assess the quality of the literature that supports cause-and-effect relations between iodine supplementation during pregnancy or the periconceptional period and the growth and development of children. As such, we focused our inclusion criteria on intervention trials that were controlled and had a random or quasirandom allocation. Despite the relatively broad inclusion criteria, only 2 of the 8 included RCTs reported limited clinical outcome data including the birth rate, birth anthropometric measures, childhood growth rate, 15-y survival, and development, and both trials were conducted in regions of severe iodine deficiency with a high incidence of endemic goiter and cretinism (17, 21). One of these trials reported a clear reduction in cretinism (21) and was a major stimulus to the eradication of cretinism worldwide through the resulting programs of salt iodization. However, what was not clear from the available data was whether prenatal or periconceptional iodine supplementation improves developmental outcomes of children in the absence of overt or frank iodine deficiency. Surprisingly, in both trials conducted in regions of severe iodine deficiency, the IQ, developmental quotient, and other nonstandardized assessments of cognitive development of noncretinous children did not differ between children whose mothers were in the iodine group and women in the placebo group (17, 21). Although there was some evidence of better motor function in children of iodine-supplemented mothers, in nonstandardized assessments (15), higher rates of developmental advantages and lower rates of developmental deficits in children of iodine-supplemented mothers were only seen after post–random-assignment exclusions on small sample sizes selectively followed up, which may have been subject to bias (22, 25). No developmental outcomes were available from children whose mothers participated in the 6 trials conducted in regions of mild to moderate iodine deficiency.

The paucity of data from controlled iodine intervention trials with sufficient statistical power to show causal relations between iodine supplementation and developmental outcomes in children left us with cohort comparisons and other study designs that inferred causation through association. Although some of these studies suggested that mild to moderate iodine deficiency in pregnant women is associated with impaired cognitive performance of children (29–32), another recent study showed that children whose mothers took iodine supplements of ≥150 μg/d in pregnancy had a 1.5- and 1.7-fold increase in odds of

TABLE 4
Summary of risk-of-bias assessment for included studies[1]

First author, year of publication (reference)	Random sequence generation	Allocation concealment	Blinding of participants/ personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Studies in regions of severe iodine deficiency							
Kevany, 1969 (17)	H	H	U	U[2]	U[3]	U	U[4]
Pretell, 1972 (26)							
Pretell, 1974 (24)							
Pretell, 1994 (25)							
Pharoah, 1971 (21)	H	H	U[5]	U[5]	H	U	H
Connolly, 1979 (15)							
Pharoah, 1987 (22)							
Pharoah, 1991 (23)							
Studies in regions of mild to moderate iodine deficiency							
Glinoer, 1995 (16)	U	U	L	L	U	U	U
Liesenkötter, 1996 (18)	H	H	U	L	U	U	U
Nøhr, 2000 (19)	U	U	L	L	U	U	L
Pedersen, 1993 (20)	U	U	H	L	U	U	L
Romano, 1991 (27)	U	U	U	L	L	U	L
Silva, 1981 (28)	H	H	U	U	H	U	U

[1] L, low risk of bias; H, high risk of bias; U, unclear risk of bias.
[2] Risk of bias was that assigned to the original trial (17). In 2 of the reported follow-ups (25, 26), it was specified that all investigators were unaware of the injection status of the subjects.
[3] Risk of bias was that assigned to the original trial (17). In the 3 reported follow-ups, outcomes were not assessed in all participants and their offspring.
[4] Risk of bias was that assigned to the original trial (17). In the 3 reported follow-ups, some of the participants had been reinjected.
[5] Risk of bias was that assigned to the original trial (21). In the 1979 follow-up (15), it was specified that the mother and person who administered tests were not aware of the injection status.

psychomotor and mental scores <85, respectively, in the Bayley Psychomotor Developmental Index at 1 y of age compared with in women who those who took <100 μg/d (33). These disparate findings warrant additional investigations in appropriately designed RCTs in areas of mild to moderate iodine deficiency as well as in areas of iodine sufficiency to allow a full investigation of potential benefits and risks of iodine supplementation according to background iodine status. However, there is intense debate about whether such trials are ethical because of the widespread recommendation for iodine supplements to be taken from preconception through to lactation and for all prenatal supplements to contain iodine (34, 35).

The increasing concern of scientists and clinicians that mild to moderate iodine deficiency in pregnancy may adversely affect the cognitive development of children has also been supported by studies that showed that lower maternal thyroxine and/or higher maternal TSH in pregnancy were associated with lower IQ in children (36, 37). However, a recent RCT that involved >21,000 pregnant women showed that correction for low thyroxine or high TSH with thyroxine supplements in early pregnancy did not improve the IQ of children at 3 y of age (38). The contrasting findings between observational studies and RCTs are not uncommon and highlight that typical statistical adjustments of potential confounders in observational studies are likely to be inadequate to capture the full extent of influences of social and environmental factors (39).

Our systematic review was conducted according to contemporary best practice and highlights the paucity of relevant and quality RCTs to assess the efficacy and safety of prenatal and periconceptional iodine supplementation in today's society where most regions of the world are classified with either mild to moderate iodine deficiency or are iodine sufficient. Despite this lack of quality evidence regarding the effect of iodine supplementation in pregnancy on the growth and development of children, routine iodine supplementation in pregnancy has been recommended by leading health authorities worldwide. Surprisingly, the process that led to the iodine recommendation is in contrast to the folate recommendation, which was made after several RCTs and a systematic review with a meta-analysis of RCTs confirmed its efficacy and safety (40).

Routine iodine supplementation in pregnancy may not be without risk. The safe upper limit in pregnancy is uncertain because the fetal thyroid is vulnerable to iodine excess (41). Congenital hypothyroidism in newborns has been reported in mothers who had an excessive dietary intake of iodine during pregnancy (42, 43). In addition, a recent study reported that iodine supplementation ≥150 μg/d in pregnancy was associated with poorer mental and psychomotor achievements of infants (33). The view that iodine supplements at the dose recommended (150–200 μg/d) are safe stems from the fact that these doses are well below the recommended upper intake limit of 600–1100 μg/d (44, 45). Results of RCTs currently under way in areas of mild to moderate iodine deficiency that aim to determine whether prenatal iodine supplementation improves maternal and neonate thyroid function, pregnancy outcomes, infant growth, and cognitive performance should contribute to these areas of uncertainty (46, 47).

In conclusion, although our review indicates that new RCTs of iodine supplementation in pregnancy with outcomes addressing childhood development are necessary to assess efficacy and safety, the conduct of such trials may not be feasible in population groups in whom iodine supplementation is widely practiced. In this context, the focus should be on monitoring and evaluating the safety of the practice to ensure it does no harm. In the absence of RCTs, prospective cohort studies that assess maternal iodine intake and biomarkers of iodine status in pregnancy on clinical outcomes including the growth and development of children are important to evaluate the safety of the practice and determine the doses of iodine associated with minimum risk.

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