European Journal of Clinical Nutrition (2013) **67,** 481–484

www.nature.com/ejcn

REVIEW

Monitoring and effects of iodine deficiency in pregnancy: still an unsolved problem?

EN Pearce

Iodine is required for the production of thyroid hormone. Thyroid hormone affects many metabolic processes in the body, including maturation of the central nervous system. In early pregnancy, the fetus is dependent on maternal thyroid hormone for normal brain development. If iodine deficiency leads to inadequate production of thyroid hormone during pregnancy, irreversible brain damage can result in the fetus. Therefore, achieving adequate iodine nutrition during pregnancy is an important public health objective. Although there have been tremendous gains over the last several decades in our understanding of the effects of iodine deficiency in pregnancy and how to combat them, a number of questions remain about how best to monitor the iodine status of pregnant populations, the effects of mild to moderate iodine deficiency on maternal and child outcomes, the safe upper limit of daily iodine intake in pregnant women and the risks and benefits of iodine supplementation for mildly iodine-deficient pregnant women.

European Journal of Clinical Nutrition (2013) **67,** 481–484; doi:10.1038/ejcn.2012.215; published online 16 January 2013

Keywords: iodine; thyroid; pregnancy

INTRODUCTION

Iodine is required for production of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3). Thyroid hormone affects many metabolic processes in the body, including maturation of the central nervous system. In early pregnancy, the fetus is dependent on maternal thyroid hormone for normal brain development.[1,2] If iodine deficiency leads to inadequate production of thyroid hormone during pregnancy, irreversible brain damage can result in the fetus. Therefore, achieving adequate iodine nutrition during pregnancy is an important public health objective.

Dietary iodine requirements are higher in pregnancy than they are for nonpregnant adults due to several major changes in thyroid physiology. Early in pregnancy, maternal thyroid hormone production increases by ~50% in response to increased levels of serum thyroxine-binding globulin (resulting from increased serum estrogen levels), to stimulation of thyroid-stimulating hormone (TSH) receptors by human chorionic gonadotropin and to increased placental inner ring deiodinase activity enhancing the degradation of T4 and T3 to inactive metabolites.[3,4] In addition, some maternal iodine and thyroid hormone are transferred to the fetus. The fetal thyroid gland begins to develop by the 12th week of gestation but cannot produce thyroid hormone until approximately the 20th week of gestation. Before this time, maternal thyroxine (T4) that can traverse the placenta in small amounts, is essential for normal fetal development. Another reason for increased iodine requirements in pregnancy is the increase in maternal glomerular filtration rate. As iodine is passively excreted, increased renal glomerular filtration results in increased losses of ingested iodine.[5]

To meet the increased dietary iodine requirements during pregnancy, the World Health Organization (WHO) recommends ~250 μg iodine intake daily for pregnant and lactating women.[6] The United States Institute of Medicine's recommended daily allowance for iodine is 220 μg during pregnancy and 290 μg during lactation, higher than the 150 μg daily recommended for nonpregnant adults.[7]

Although there have been tremendous gains over the last several decades in our understanding of the effects of iodine deficiency in pregnancy and how to combat them, a number of questions remain about how best to monitor the iodine status of pregnant populations, the effects of mild to moderate iodine deficiency on maternal and child outcomes, and the risks and benefits of iodine supplementation for mildly iodine-deficient pregnant women.

EFFECTS OF IODINE DEFICIENCY IN PREGNANCY

Both maternal and fetal hypothyroidism can result from severe iodine deficiency in pregnancy. Severe iodine deficiency is associated with adverse obstetric outcomes including prematurity, spontaneous abortion and stillbirth.[6] In addition, TSH stimulation in iodine-deficient pregnant women can lead to goiter.[8,9] European studies examining changes in maternal thyroid volume across pregnancy found that in iodine-sufficient areas, thyroid volume increases by 10–15% during pregnancy,[10,11] although in areas with mild to moderate iodine deficiency thyroid volume increases by about 25% over the course of gestation.[3,12]

Based on animal models, even mild and transient maternal hypothyroxinemia during pregnancy can disrupt neuronal migration in the fetus.[1,13] Severe deficiency in circulating iodine, therefore, is associated with adverse effects on the fetus including congenital anomalies, decreased intelligence and neurological cretinism (which includes spasticity, deaf mutism, mental deficiency, and squint).[14] Despite global efforts toward

Section of Endocrinology, Diabetes and Nutrition, Boston University School of Medicine, Boston, MA, USA. Correspondence: Dr EN Pearce, Section of Endocrinology, Diabetes and Nutrition, Boston University School of Medicine, 88 East Newton Street, Evans 201, Boston, MA 02118, USA.
E-mail: elizabeth.pearce@bmc.org
Received 17 September 2012; accepted 18 December 2012; published online 16 January 2013

universal salt iodization, iodine deficiency remains the leading preventable cause of mental retardation worldwide.[15] Severe maternal iodine deficiency has also been linked to more subtle intellectual impairment in children. A 2005 meta-analysis of Chinese studies found that IQ was, on average, 12.5 points lower in iodine-deficient children than in children with adequate iodine intake.[16]

The effects of mild to moderate iodine deficiency are less well understood than those of severe iodine deficiency. In a landmark study, Haddow *et al.*[17] assessed 7–9-year-old children of women with mild second-trimester TSH elevations and found that IQ scores averaged 7 points lower than that in the children of matched euthyroid women. Pop *et al.*[18] found that the psychomotor scores of 10-month-old infants of women with first trimester hypothyroxinemia were lower than those of infants of euthyroid women. Henrich *et al.*[19] found that lower maternal FT4 was associated with an increased risk of expressive language delay at age 18 and 30 months in 3659 children. All of these observational studies demonstrate the impact of even mild maternal thyroid hypofunction on fetal neurodevelopment. However, because most of these studies were conducted in iodine-sufficient areas, the thyroid hypofunction cannot be directly attributed to iodine deficiency.

MONITORING FOR IODINE DEFICIENCY IN PREGNANCY

There are several accepted methods used for the monitoring of population iodine sufficiency.[14] The primary route of iodine excretion is through the kidney,[20] which accounts for $>90\%$ of ingested iodine.[21] Therefore, random spot urinary iodine concentration measurements[22] reflect recent dietary iodine intake. However, thresholds for urinary iodine concentrations have been identified for populations, but not for individuals, given significant day-to-day variation of individuals' iodine intake.[23,24] Optimal population iodine intake is defined by median urinary iodine concentrations 100–199 μg/l in nonpregnant women and 150–249 μg/l during pregnancy.[6] The iodine status of school-aged children has been used as a surrogate for iodine sufficiency of overall populations. However, an analysis of recent surveys found that 47% of the time, when regional surveys of school-aged children or non-pregnant women demonstrated adequate iodine intake, iodine intake was insufficient in pregnant women.[25] This suggests that surveys may need to specifically target pregnant women and other vulnerable populations.

Serum TSH and thyroglobulin levels increase over weeks to months of iodine deficiency, though these concentrations often remain in the normal range and are thus not a good measure of mild iodine deficiency. Goiter size, assessed by palpation or ultrasonography, may also be used to assess long-term iodine sufficiency in populations. The WHO has established international reference ranges for serum thyroglobulin and thyroid gland volumes to be used in the monitoring of iodine deficiency in school-aged children,[26,27] but there are currently no guidelines for monitoring of these parameters in pregnant populations.[28]

EFFECTS OF IODINE SUPPLEMENTATION IN PREGNANCY

The effectiveness of iodine supplementation for severely iodine-deficient pregnant women is well established. A blinded, placebo-controlled clinical trial begun in the 1960s in Papua New Guinea demonstrated that pre-conception supplementation of severely iodine-deficient women (median urinary iodine concentration <20 μg/l) with iodinated oil eliminated the risk of cretinism and improved offspring cognitive function and survival.[29] These findings have subsequently been replicated in many regions of the world.[30]

The efficacy of iodine supplementation for mildly to moderately iodine-deficient pregnant women has been less well studied. Six controlled trials of iodine supplementation in moderately iodine deficient pregnant European women have been published, although doses and timing of iodine supplementation varied and effects on child development were not assessed.[31–36]

Romano *et al.*[31] examined the effects of supplementation with 120–180 μg per day iodine starting in the first trimester of pregnancy. In all, 17 Italian women (baseline median urinary iodine concentration 37 μg/l) were randomized to treatment and compared to with controls (urinary iodine concentration 31 μg/l). In the untreated women, but not in the treated group, thyroid size increased significantly over the course of pregnancy; there were no changes in maternal serum TSH. Pederson *et al.*[32] treated 28 Danish women (median urinary iodine concentration 55 μg/l) with 200 μg per day of iodine starting at 17–18 weeks gestation. Compared with 26 controls, the treated group had decreased maternal thyroid volumes, maternal and cord blood thyroglobulin, and maternal TSH, but there was no difference in maternal or cord blood T3, T4 or free T4. In Belgium, Glinoer *et al.*[33] randomized 180 women (median urinary iodine concentration 36) to treatment with placebo, 100 μg/day of potassium iodide, or 100 μg day of potassium iodide with L-T4, starting at a mean 14-week gestation. Those treated with potassium iodide alone had decreased maternal and neonatal thyroid volumes compared with controls, decreased maternal TSH and thyroglobulin levels, and decreased neonatal thyroglobulin. There was no observed effect on maternal or cord blood T3, free T4 or T3/T4 ratio.

Liesenkotter *et al.*[34] treated 38 German women (median urinary iodine concentration 53 μg/g creatinine) with 300 μg potassium iodide daily starting at 10–12 weeks gestation. Compared with 70 untreated women, there was a decrease in neonatal thyroid volume, but no difference in maternal thyroid volume. There was no effect of treatment on maternal TSH, T3, T4, free T4 or thyroglobulin, and no effect on neonatal TSH. Nohr and Laurberg[35] assessed maternal and neonatal thyroid function at delivery in 49 Danish women who had taken a multivitamin containing 150 μg iodine daily compared with 95 women who had not received iodine supplements. Maternal TSH was lower but cord blood TSH was higher in the supplemented group; free T4 was higher in both supplemented mothers and infants, and serum thyroglobulin was lower in the supplemented mothers and infants. There were no observed effects on T3, T4, free T4 index or thyroglobulin antibody levels. Antonangeli *et al.*[36] randomized 86 Italian women (median urinary iodine concentration 74 μg/g creatinine) to treatment with either 50 or 200 μg daily iodine starting at week 10–16 of pregnancy. There were no significant differences in maternal TSH, FT4, thyroglobulin, free T3 or thyroid volume between the groups.

Three uncontrolled and unrandomized Spanish studies have examined the effects of iodine supplementation in moderately iodine-deficient pregnant women on neurocognitive outcomes in offspring. Berbel *et al.*[37] supplemented 92 women with 200 μg per day of potassium iodide starting at 4–6 weeks gestation, 102 women starting at 12–14 weeks gestation and 151 women (mean urinary iodine concentration 75 μg/l) only after delivery. Supplementation was continued in all women until the end of lactation. At term, FT4 was higher in the two supplemented groups, whereas serum TSH values did not differ. Neurocognitive testing was carried out using the Brunet–Lézine scale in 44 selected children at 18 months of age. Mean developmental quotients were higher in children whose mothers were supplemented with iodine starting in week 4–6 of pregnancy than in children of mothers from the other two groups, and there was no significant difference between the developmental quotients of the children whose mothers were supplemented starting at week 10–12 and those who were supplemented only starting at delivery. Velasco *et al.*[38] demonstrated that infants of Spanish mothers who had received oral 300 μg potassium iodide supplements daily during pregnancy and lactation had higher Bayley Psychomotor Development scores

at 3–18 months of age than infants whose mothers did not receive iodine supplements. Finally, Murcia *et al.*[39] and colleagues assessed iodine intake from diet and supplements in pregnant women in relation to maternal and neonatal thyroid function and infant neurodevelopment. In contrast to the two previous studies, they found decreased psychomotor development index scores in children of the mothers who ingested 150 μg or more iodine daily from supplements.

Two randomized controlled trials in areas of relatively mild iodine deficiency have examined the effects of iodine supplementation on neurocognition in school-aged children. Zimmermann *et al.*[40] supplemented moderately iodine-deficient 10–12-year-old Albanian children with 400 mg iodine as iodized oil vs placebo and found that at 24 weeks, iodine treatment had significantly improved performance in four of seven neurocognitive tests. Gordon *et al.*[41] randomized 10–13 year-old mildly iodine-deficient New Zealand children to a daily 150 μg iodine supplement vs placebo. After 28 weeks, the supplemented children had significantly higher scores for two of four cognitive subtests.

Randomized controlled clinical trials examining the effects of iodine supplementation for mildly- to moderately iodine-deficient pregnant women are currently ongoing in Thailand and India, and should provided much-needed data regarding both maternal effects and effects on infant neurodevelopment.[42]

EFFECTS OF IODINE EXCESS IN PREGNANCY

The safe upper limit of iodine intake in pregnancy is uncertain. Following exposure to high iodine levels, the synthesis of thyroid hormone is normally transiently inhibited by a mechanism known as the acute Wolff–Chaikoff effect.[43] If high iodine exposure persists, the thyroid is able to 'escape' from the acute Wolff–Chaikoff effect within a few days.[44] This is accomplished in part by downregulating the expression of the sodium iodide symporter, decreasing the transport of iodine into the thyroid.[45] Although most pregnant women can maintain normal thyroid function in the setting of a large iodine load, women with subtle defects in thyroid hormone synthesis, such as those with Hashimoto's thyroiditis, may be unable to escape from the acute Wolff–Chaikoff effect and can develop iodine-induced hypothyroidism. Although low-dose iodine supplementation is appropriate in pregnant women with Hashimoto's thyroiditis in order to ensure that adequate iodine is transferred to the fetus, excessive iodine exposure should be avoided in such women. In addition, the fetal thyroid gland does not acquire the capacity to fully escape from the acute Wolff–Chaikoff effect until ~36 weeks gestation.[46] Therefore, a maternal iodine load could potentially selectively cause fetal hypothyroidism. We have recently reported neonatal hypothyroidism in three infants of women ingesting 12.5 mg iodine daily during gestation.[47]

The World Health Organization has proposed that an iodine intake of 500 μg per day poses no excessive risk[6] and the European Food Safety Agency and the US Institute of Medicine has recommended 600 μg/day and 1100 μg/day, respectively, as the tolerable upper limit for iodine per day[7,48] However, these maximal values are based on limited data, and more studies are needed to better define safe upper intake limits in pregnancy. In general, it is felt that the benefits of correcting iodine deficiency far outweigh the risks of supplementation as long as supplementation is not excessive.[49]

CONCLUSIONS

Overall, it is clear that repleting iodine in women in areas of severe iodine deficiency improves obstetric and child outcomes. Iodine supplementation of mildly- to moderately deficient pregnant women appears to consistently decrease maternal and neonatal thyroid volumes and thyroglobulin levels. Effects on maternal thyroid function have been mixed, with significant maternal TSH decreases with supplementation described in four of eight published studies, and increases in maternal T4 or free T4 noted in just two. In two of three uncontrolled studies where it was assessed, neurodevelopmental outcomes were improved in children whose mothers received iodine supplementation early in pregnancy. The timing of supplementation is likely to be critical. In the Velasco *et al.*[38] study, 77% of women in the treatment group began receiving iodine supplements before the 10th week of gestation, and in Berbel *et al.*,[37] the beneficial effects of iodine on offspring development appeared to be lost if supplementation was started after the 10th week of pregnancy. Prospective, controlled studies are needed to confirm these results and to better define optimal dosing strategies in moderately iodine-deficient women.

In the US, where there are concerns about mild iodine deficiency in at least a subset of pregnant women,[50] the American Thyroid Association has recommended that all women receive dietary supplements containing 150 μg iodine daily during pregnancy and lactation.[51] The Endocrine Society has recommended that all daily prenatal multivitamins include 150–200 μg iodine.[52] The World Health Organization has advocated daily oral iodine supplements or annual iodized oil supplements for pregnant women in regions, where only 20–90% of households use iodized salt.[53] However, these recommendations have not been widely adopted. At present, only 13–50% of pregnant women in Europe receive iodine-containing supplements[54] and 49% of the different prenatal multivitamin brands marketed in the US contain no iodine.[55]

Ensuring that all at-risk women receive adequate iodine intake starting pre-pregnancy or as early as possible in gestation, is an important goal. Ideally, sufficient iodine nutrition should be assured by universal salt iodization programs, which would eliminate the need for specific supplementation in pregnancy and lactation. Adequate population iodine status has also been achieved in some regions by the addition of iodine to breads or other processed foods.[15] However, even in regions where adequate iodine intake has been achieved for the overall population, as demonstrated by optimal median iodine concentrations in school-aged children, pregnant women may still be at risk of mild to moderate iodine deficiency. In such areas, iodine supplementation is recommended for all women who are pregnant or lactating. More research is needed on the effects of iodine supplementation on mild to moderate iodine deficiency especially, its effects on infant growth and neurodevelopment. The development of an individual biomarker for iodine nutritional status would provide a valuable tool for targeting iodine supplementation in pregnancy. Finally, more studies are needed to better determine safe upper intake limits for iodine in pregnant and lactating women.

CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

1 De Escobar GM, Obregon MJ, Del Rey FE. Iodine deficiency and brain development in the first half of pregnancy. *Public Health Nutr* 2007; **10**: 1554–1570.
2 Younes-Rapozo V, Berendonk J, Savignon T, Manhães AC, Barradas PC. Thyroid hormone deficiency changes the distribution of oligodendrocyte/myelin markers during oligodendroglial differentiation in vitro. *Int J Dev Neurosci* 2006; **24**: 445–453.
3 Glinoer D. The importance of iodine nutrition during pregnancy. *Public Health Nutr* 2007; **10**: 1542–1546.
4 Glinoer D. Pregnancy and iodine. *Thyroid* 2001; **11**: 471–481.
5 Dafnis E, Sabatini S. The effect of pregnancy on renal function: physiology and pathophysiology. *Am J Med Sci* 1992; **303**: 184–205.

6 World Health Organization. United Nations Children's Fund, and International Council for the Control of Iodine Deficiency Disorders. *Assessment of Iodine Deficiency Disorders and Monitoring their Elimination. A Guide for Programme Managers*. 3rd Edition, World Health Organization: Geneva, Switzerland, 2007.
7 Institute of Medicine. *Dietary Reference Intakes for Vitamin A, vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. National Academy Press: Washington DC, 2001.
8 Yoshimura M, Hershman JM. Thyrotropic action of human chorionic gonadotropin. *Thyroid* 1995; **5**: 425–434.
9 Glinoer D, de Nayer P, Bourdoux P, Lemone M, Robyn C, van Steirteghem A *et al.* Regulation of maternal thyroid during pregnancy. *J Clin Endocrinol Metab* 1990; **71**: 276–287.
10 Smyth PPA, Hetherton AM, Ryan R, O'Herlihy C. Alterations in iodine status and thyroid volume in pregnancy. In: Beckers C, Reinwein D (eds) *The Thyroid and Pregnancy*. Schattauer, Stuttgart: New York, 1991, pp 55–58.
11 Brander A, Kivisaari L. Ultrasonography of the thyroid during pregnancy. *J Clin Ultrasound* 1989; **17**: 403–406.
12 Rasmussen NG, Hornnes PJ, Hegedus L. Ultrasonographically determined thyroid size in pregnancy and post partum: the goitrogenic effect of pregnancy. *Am J Obstet Gynecol* 1989; **160**: 1216–1220.
13 Zoeller TR, Dowling AL, Herzig CT, Iannacone EA, Gauger KJ, Bansal R. Thyroid hormone, brain development, and the environment. *Environ Health Perspect* 2002; **110**: 355–361.
14 Chen ZP, Hetzel BS. Cretinism revisited. *Best Pract Res Clin Endocrinol Metab* 2010; **24**: 39–50.
15 Zimmermann MB. Iodine deficiency. *Endocr Rev* 2009; **30**: 376–408.
16 Qian M, Wang D, Wakins WE, Gebski V, Yan YQ, Li M *et al.* The effects of iodine on intelligence in children: a meta-anylsis of studies conducted in China. *Asia Pac J Clin Nutr* 2005; **14**: 32–42.
17 Haddow JE, Palomake GE, Allan WC, Williams JR, Knight GJ, Gagnon J *et al.* Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999; **341**: 549–555.
18 Pop VJ, Kuijpens JI, van Baar AL, Verkerk G, Verkerk G, van Son MM *et al.* Low maternal free thyroxine conentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clin Endocrinol* 1999; **50**: 147–148.
19 Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. *J Clin Endocrinol Metab* 2010; **95**: 4227–4234.
20 Wayne EJ, Koutras DA, Alexander WD. Excretion of iodine. In: *Clinical Aspects of Iodine Metabolism*. Blackwell: Philadelphia, PA: Oxford, 1964, pp 73–83.
21 Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. *Lancet* 2008; **372**: 1251–1262.
22 Vought RL, London WT. Iodine intake, excretion and thyroidal accumulation in healthy subjects. *J Clin Endocrinol Metab* 1967; **27**: 913–919.
23 Rasmussen LB, Ovesen L, Christiansen E. Day-to-day and within-day variation in urinary iodine excretion. *Eur J Clin Nutr* 1999; **53**: 401–407.
24 König F, Andersson M, Hotz K, Aeberli I, Zimmermann MB. Ten repeat collections for urinary iodine from spot samples or 24 h samples are needed to reliably estimate individual iodine status in women. *J Nutr* 2011; **141**: 2049–2054.
25 Wong EM, Sullivan KM, Perrine CG, Rogers LM, Peña-Rosas JP. Comparison of median urinary iodine concentration as an indicator of iodine status among pregnant women, school-age children, and nonpregnant women. *Food Nutr Bull* 2011; **32**: 206–212.
26 Zimmermann MB, Hess SY, Molinari L, De Benoist B, Delange F, Braverman LE *et al.* New reference values for thyroid volume by ultrasound in iodine-sufficient schoolchildren: a World Health Organization/Nutrition for health and development iodine deficiency study group report. *Am J Clin Nutr* 2004; **79**: 231–237.
27 Zimmermann MB, de Benoist B, Corigliano S, Jooste PL, Molinari L, Moosa K *et al.* Assessment of iodine status using dried blood spot thyroglobulin: development of reference material and establishment of an international reference range in iodine-sufficient children. *J Clin Endocrinol Metab* 2006; **91**: 4881–4887.
28 Skeaff SA. Assessing iodine intakes in pregnancy and strategies for improvement. *J Trace Elem Med Biol* 2012; **26**: 141–144.
29 Pharoah PO, Connolly KJ. A controlled trial of iodinated oil for the prevention of endemic cretinism: a long-term follow-up. *Int J Epidemiol* 1987; **16**: 68–73.
30 Zimmermann MB. Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review. *Am J Clin Nutr* 2009; **89**: 668S–672S.
31 Romano R, Jannini EA, Pepe M, Grimaldi A, Olivieri M, Spennati P *et al.* The effects of iodoprophylaxis on thyroid size during pregnancy. *Am J Obstet Gynecol* 1991; **164**: 482–485.
32 Pedersen KM, Laurberg P, Iversen E, Knudsen PR, Gregersen HE, Rasmussen OS *et al.* Amelioration of some pregnancy-associated variations in thyroid function by iodine supplementation. *J Clin Endocrinol Metab* 1993; **77**: 1078–1083.
33 Glinoer D, De Nayer P, Delange F, Lemone M, Toppet V, Spehl M *et al.* A randomized trial for the treatment of mild iodine deficiency during pregnancy: maternal and neonatal effects. *J Clin Endocrinol Metab* 1995; **80**: 258–269.
34 Liesenkötter KP, Göpel W, Bogner U, Stach B, Grüters A. Earliest prevention of endemic goiter by iodine supplementation during pregnancy. *Eur J Endocrinol* 1996; **134**: 443–448.
35 Nøhr SB, Laurberg P. Opposite variations in maternal and neonatal thyroid function induced by iodine supplementation during pregnancy. *J Clin Endocrinol Metab* 2000; **85**: 623–627.
36 Antonangeli L, Maccherini D, Cavaliere R, Di Giulio C, Reinhardt B, Pinchera A *et al.* Comparison of two different doses of iodide in the prevention of gestational goiter in marginal iodine deficiency: a longitudinal study. *Eur J Endocrinol* 2002; **147**: 29–34.
37 Berbel P, Mestre JL, Santamaría A, Palazón I, Franco A, Graells M *et al.* Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. *Thyroid* 2009; **19**: 511–519.
38 Velasco I, Carreira M, Santiago P, Muela JA, García-Fuentes E, Sánchez-Muñoz B *et al.* Effect of iodine prophylaxis during pregnancy on neurocognitive development of children during the first two years of life. *J Clin Endocrinol Metab* 2009; **94**: 3234–3241.
39 Murcia M, Rebagliato M, Iñiguez C, Lopez-Espinosa MJ, Estarlich M, Plaza B *et al.* Effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 year of age. *Am J Epidemiol* 2011; **173**: 804–812.
40 Zimmermann MB, Connolly K, Bozo M, Bridson J, Rohner F, Grimci L. Iodine supplementation improves cognition in iodine-deficient schoolchildren in Albania: a randomized, controlled, double-blind study. *Am J Clin Nutr* 2006; **83**: 108–114.
41 Gordon RC, Rose MC, Skeaff SA, Gray AR, Morgan KM, Ruffman T. Iodine supplementation improves cognition in mildly iodine-deficient children. *Am J Clin Nutr* 2009; **90**: 1264–1271.
42 Melse-Boonstra A, Gowachirapant S, Jaiswal N, Winichagoon P, Srinivasan K, Zimmermann MB. Iodine supplementation in pregnancy and its effect on child cognition. *J Trace Elem Med Biol* 2012; **26**: 134–136.
43 Wolff J, Chaikoff IL. The temporary nature of the inhibitory action of excess iodine on organic iodine synthesis in the normal thyroid. *Endocrinol* 1949; **45**: 504–501.
44 Eng PH, Cardona GR, Fang SL, Previti M, Alex S, Carrasco N *et al.* Escape from the acute Wolff-Chaikoff effect is associated wit ha decrease in thyroid sodium/iodide symporter messenger ribonucleic acid and protein. *Endocrinology* 1999; **140**: 3404–3410.
45 Markou K, Georgopoulos N, Kyriazopoulou V, Vagenakis AG. Iodine-induced hypothyroidism. *Thyroid* 2001; **11**: 501–510.
46 Bartalena L, Bogazzi F, Braverman LE, Martino E. Effects of amiodarone administration during pregnancy on neonatal thyroid function and subsequent neurodevelopment. *J Endocrinol Invest* 2001; **24**: 116–130.
47 Connelly KJ, Boston BA, Pearce EN, Sesser D, Snyder D, Braverman LE *et al.* Congenital hypothyroidism caused by excess prenatal maternal iodine ingestion. *J Pediatr* 2012; **161**: 760–762.
48 Opinion of the scientific committee on food on the tolerable upper intake level of iodine; 2002. Available from http://ec.europa.eu/food/fs/sc/scf/out146_en.pdf.
49 Braverman LE. Adequate iodine intake—the good far outweighs the bad. *Eur J Endocrinol* 1998; **139**: 14–15.
50 Perrine CG, Herrick K, Serdula MK, Sullivan KM. Some subgroups of reproductive age women in the US may be at risk for iodine deficiency. *J Nutr* 2010; **140**: 1489–1494.
51 Stagnaro-Green A, Abalovich M, Alexander EK, Alexander E, Azizi F, Mestman J *et al.* Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid* 2011; **21**: 1081–1125.
52 De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH *et al.* Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2012; **97**: 2543–2565.
53 WHO SecretariatAndersson M, de Benoist B, Delange F, Zupan J. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. *Public Health Nutr* 2007; **10**: 1606–1611.
54 Zimmermann MB. Iodine supplementation of pregnant women in Europe: a review and recommendations. *Eur J Clin Nutr* 2004; **58**: 979–984.
55 Leung AM, Pearce EN, Braverman LE. Iodine content of prenatal multivitamins in the US. *N Engl J Med* 2009; **360**: 939–940.