Title

Contemporary challenges to iodine status and nutrition – the role of foods, dietary recommendations, fortification and supplementation.

Shortened Title

Improving iodine status

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Abstract

Iodine deficiency (ID) in women of childbearing age remains a global public health concern, mainly through its impact on fetal and infant neurodevelopment. While iodine status is improving globally, ID is still prevalent in pregnancy, when requirements increase. More than 120 countries have implemented salt iodisation and food fortification, strategies that have been partially successful. Supplementation during pregnancy is recommended in some countries, and supported by the WHO when mandatory salt iodisation is not present. The UK is listed between the ten countries with the lowest iodine status globally and ~60% of pregnant women do not meet the WHO recommended intake. Without mandatory iodine fortification or recommendation for supplementation in pregnancy, the UK population depends on dietary sources of iodine. Both women and healthcare professionals have low knowledge and awareness of iodine, its sources or its health role. Dairy and seafood products are the richest sources of iodine and their consumption is essential to support adequate iodine status. Increasing iodine through the diet might be possible if iodine-rich foods get repositioned in the diet, as they now contribute towards only ~13% of the average energy intake of adult women. This review examines the use of iodine-rich foods in parallel with other public health strategies, to increase iodine intake and highlights the rare opportunity in the UK for randomised trials, due to the lack of mandatory fortification programs.

Mild iodine insufficiency and public health

Iodine is essential for the synthesis of the thyroid hormones T3 (L-triiodothyronine) and T4 (L-tetraiodothyronine or thyroxine)[1], and iodine deficiency (ID), through impairment of synthesis, can lead to a range of adverse effects, defined in the 1980s as Iodine Deficiency Disorders (IDD). IDD encompass a range of disorders caused by iodine insufficiency, affecting the different lifecycle stages with a variety of symptoms, including hypothyroidism, stillbirth, impaired mental function, congenital anomalies and iodine-induced hyperthyroidism[2]. ID is the most preventable cause of brain retardation for the infant[3] and consequences range from loss of intelligence quotient (IQ) to cretinism. The main visible sign of severe ID is goiter.

Impairment of fetal / infant neurological development is irreversible and has lifelong consequences. Neuronal myelination and migration both require thyroid hormones during the early stages of pregnancy and infancy, which depend on iodine availability[4]. Insufficient intake of iodine during pregnancy can adversely affect both maternal thyroid health (iodine-induced hyperthyroidism or hypothyroidism) and the infant neurological development[3; 5]. In its most extreme form, deficiency can lead to cretinism, growth retardation and intellectual impairments, pregnancy losses as well as increased mortality in infants[3]. Children born to moderately iodine deficient mothers can have neurological and psychological problems, hyperactivity and decreased IQ scores[5]. In a meta-analysis of both intervention and cohort studies, ID in children aged 5 years old and under caused 6.9-10.2 points lower IQ, although high heterogeneity in the evidence selected calls for cautious interpretation[6]. The same study concluded that maternal iodine status is positively associated with infant neurological development and that supplementation with iodine (via intramuscular injection, which is seldom nowadays) appears beneficial in early pregnancy compared to late pregnancy (effect size for mental development d = 0.82). After birth, if the infant is exclusively breast fed, the mother remains its sole source of iodine until weaning, with the offspring potentially exposed to suboptimal iodine levels for at least 13-15 months, 29-33% of the critical first 45 months of neurodevelopment (depending on weaning age, subsequent complementary feeding)[6].

Iodine insufficiency, even marginal (urinary iodine concentration in population 50-99 μg/l), has been shown to affect children cognition and their school performance in the UK. The offspring of mothers taking part in ALSPAC study had IQ in the lowest quartile (odds ratio 1.58, 95% CI 1.09-2.30; p=0.02) at 8 years when maternal urinary iodine concentration in pregnancy had been below 150 μg/g of creatinine[7]. The use of a single urine iodine measurement only provides a crude categorisation of iodine exposure, which nonetheless resulted in an unexpected outcome for 21st century Britain. In epidemiological studies, the median urinary iodine concentration of a population is the commonly used biomarker for determination of iodine status, as proposed by the WHO[3]. Table 1 shows the cut-off points for categorisation of iodine status based on urine samples, which provides an indication of iodine intake in the short-term. Other biomarkers of iodine status measured in blood include thyroglobulin (Tg), representative of longer term iodine intake[8], and TSH, which is rarely useful outside of more severe forms of deficiency[8; 9]. While the validation of Tg as a marker of iodine status is still ongoing (with previously proposed Tg cut off for iodine sufficiency of 13 µg/l now understood not to be always applicable) [8], a range of 4–40 µg/l has been described for iodine sufficiency in school-age children[10; 11].

After reports of insufficient status in schoolgirls in 2011, (median urinary iodine concentration 80.1 µg/l, IQR 56.9–109.0), mild iodine insufficiency in the UK is a renewed public health concern [12]. Previously believed to be iodine-replete, women in the UK have been shown to be iodine insufficient at population level[13; 12; 14]. Our work in females of childbearing age (cross-sectional survey in Scotland) also established that this population is iodine insufficient (median 75 µg/l)[14]. To address this issue in the UK and globally, we must examine the role of awareness, dietary choices and public health strategies.

Dietary choices and iodine intake

Dietary choices are critical for an adequate iodine intake. The main dietary sources of iodine in the UK are marine fish, seafood, seaweed and dairy products, and their consumption varies among women (Figure 1)[15]. In most countries, the main dietary source of iodine is fortified salt[16]. To assess habitual iodine intake with minimal participant burden, a short food frequency questionnaire (FFQ) was previously developed and validated[17]. We found that 60% of pregnant women do not meet the 250 µg/day WHO recommended iodine intake in the UK[18]. Many believe that iodine status is potentially compounded by consumption of cruciferous vegetables and soya products (collectively known as goitrogenic foods), evidence in humans is weak. In a crossover intervention in healthy women of childbearing age with low habitual iodine intake, we did not find differences in thyroid function in women with increased intake of those foods[19].

Milk and dairy products

We and others have shown that milk is the main dietary source of iodine in the UK[15]. Milk and milk products contribute to 38% of the iodine intake[20] in non-pregnant adults. In lactating and pregnant women, milk alone contributes toward 38% and 40% of the dietary iodine intake[21]. Meanwhile, in pregnancy iodine is also provided by other dairy (31%)[18].

Iodine in milk naturally occurs in small levels, and most of the iodine in milk comes from indirect fortification through animal feeds and iodine-containing antiseptic use. Seasonality and farming practices affect milk iodine concentration (ranging from 152 to 256 ng/g), and summer and organic milk have been found to have lower iodine compared to winter and conventional milk (organic milk 26-42% lower than conventional)[22; 23]. Processing can also affect iodine; Ultra High Temperature (UHT) milk has 30% lower iodine compared to conventional milk, although the milk fat content has no effect[24]. Plant-based milk alternatives do not contain iodine naturally and are rarely fortified, resulting in very low iodine concentrations (3.1 ± 2.5 μg/250 ml; approximately 2% of the iodine content of conventional milk). Long-term consumption of non-conventional, non-cow's milk can place individuals at risk of iodine insufficiency[25; 23].

The current UK recommendations for dairy products intake lack specificity in comparison to the recommendations provided by other countries (e.g. United States, New Zealand, Japan, Australia), that have set easy-to-use portion size guidance for dairy intakes. The recommendation in the updated "Eatwell Guide" is to *"have some dairy or dairy alternatives (such as soya drinks); choosing lower fat and lower sugar options*" which does not differ from the previous UK recommendations, although the dairy products part in the depicted form of the new "Eatwell Guide" is slightly smaller compared to the previous "Eatwell Plate"[26]. In addition, the serving size for milk and other dairy products is not specified[27] with no differentiation in the dairy product type suggested (apart from the recommendation of choosing lower fat and sugar). The inclusion of dairy alternatives to the recommendation is also concerning for iodine status (lacking for example in protein, calcium, iodine, riboflavin and vitamin B12 if they are not fortified) is also concerning [28; 25; 29].

The identification of barriers, facilitators and perceptions towards iodine-rich foods consumption is important, considering their potential input in increasing iodine intake. Perceptions of healthiness are closely related to dietary behaviour and food choice; attitudes to healthy eating are influenced by factors such as sensorial characteristics, culture, food availability, child feeding and energy density[30]. Consumer perceptions towards aspects of dairy products have been previously investigated - with their perceived healthiness ranked as *relatively healthy*[31]. Women's perceptions of dairy foods, examined through focus groups, highlighted awareness of dairy high calcium content and high fat content. The taste of some products, including low fat, was reported as unsatisfying. Convenience was reported as an important factor, potentially partly compounded by increased cost of such products. Dairy products, however, are considered as staples in the everyday life of many, and neither cost nor convenience would not affect purchasing decision [32]. Other drivers of dairy food choices include not only taste, but also other family member's preferences and perceived health benefits[33; 34] as well as gender, age and socioeconomic status, which also determine the acceptance of functional and enriched foods[35].

Fish and seafood

Fish is a rich natural source of dietary iodine, and it is the main contributor to the UK dietary iodine intake after dairy, contributing towards 11% of the intake in non-pregnant adults [20; 15], and 24% in pregnancy[18].

The diversity of fish and seafood products creates a variety of food choices with a spectrum of iodine contents. White fish, such as haddock and cod, contains more iodine than oil-rich fish (approximately 48 μg/100 grams in oily fish versus 105 μg/100 grams in white fish) [36]. Iodine also varies within species and decreases from the skin to the inner part of the fish fillets, with levels 20 times higher is the skin of marine species such as cod [37]. Marine fish contains the highest amounts of iodine, ranging from 0.4 to 6.9 μg/g, which is also approximately 6-fold higher compared to freshwater fish[38]. Cooking can affect the iodine content of fish, with losses varying in average from 20% in fried fish, to 23% in grilled fish and 58% in boiled fish [39]. Other seafood (including prawns, crab, lobster) have an average iodine content of 92 μg/100 grams and are also a good source of iodine.

Seafood consumption is important both in pregnancy and in the general population as it provides iodine, but also omega 3 fatty acids, protein and other micronutrients such as vitamin D, vitamin A and selenium, In the UK, the recommendation is to consume two portions of fish per week (2 x 140g), one of which should be oily[26]. According to the NDNS, oily fish intake still remains lower than once weekly[15]. White fish is consumed more often compared to oil rich fish [40]. During pregnancy, women should consume “at least” two portions of fish per week, one of which should be from oil-rich fish. However, simultaneous advice against consuming types of fish with potentially harmful levels of mercury, as well as raw shellfish due to harmful bacteria and risk of poisoning, may create confusion over the recommendation for fish intake.

The theory of planned behaviour (TPB), used in the context of intention and frequency of fish consumption in Iran, concluded that the perceived behavioural control and the intention to eat fish predicts the frequency of fish consumption (R^2=0.58, F=223.1, p<0.001)[41]. Whether people include fish in their diet depends on drivers of food choice. There is a gap between the scientific evidence of risks and benefits related to fish and seafood consumption and actual beliefs and perceptions of consumers [42]. In our interviews with women in the perinatal period, taste and heartburn have been described as the main drivers for inclusion or exclusion of fish, seafood and dairy products in the diet.

Fish consumption is only well accepted during pregnancy by less than 20% of the population, with taste and smell the main barriers(43). Most believe that eating fish is beneficial for health (94%; survey of 329 people, the United States (US) with benefits attributable to omega-3 oils according to 45%. A substantial proportion also perceived conception to be "risky" (70%, main risk attributable to mercury content, according to 24%)(44). In five European countries, fish consumption was associated with country-related traditions and habits, which outweighed perceptions of risks and benefits(45). Ethical factors also feature in the choice to consume fish, with Danish respondents willing to pay more for welfare fish than farmed fish (48%)(46).

Seaweed

Seaweed is a rich iodine source, suitable for vegan and vegetarian population. The iodine level in seaweed products if very broad (range 11-6118 μg/g of dried seaweed) and could lead to an iodine excess - beyond the European Tolerable Upper Limit (TUL) of 600 μg daily. Labelling of seaweed-containing products is generally poor, with limited information on iodine content or seaweed specie on the product packages(47). Only 10% of the seaweed-containing products stated information regarding iodine content, and 18% enabled its estimation. A total of 26 products could lead to an intake above the adult TUL if consumed(47). While sushi dishes are reported to be consumed at least once per year by 45% of the population(48), they mostly contain Nori seaweed, with a lower iodine content of 16 μg of iodine per gram (an average sheet of Nori being approximately 3 grams)(49).

Iodine knowledge and awareness

The low profile of iodine in the UK Public Health and media arena can potentially explain the low knowledge and awareness about the nutrient amongst mothers and healthcare professionals (HCPs). Pregnant women receive general dietary guidance during pregnancy, which is usually delivered by the community midwives during the first antenatal care appointment. These recommendations focus on following a balanced diet with limited specific practical recommendations on foods to include/increase/decrease/exclude or portion sizes(50). The first antenatal appointment usually happens around the 12th week of pregnancy, with content of the discussion varying between cases and depends on both midwife's and woman's knowledge, education and personal interest in nutrition(43).

Healthcare professionals

HCPs have low awareness of iodine in childbearing age, its importance, sources and recommendations. Recommendations in the US include daily prenatal vitamins containing 150 μg of iodine during preconception, pregnancy, and lactation. Obstetricians and midwives (web-based survey, n=476) recognised (60%) that supplementation in childbearing age and pregnancy is useful, but most (75%) reported to rarely or never prescribe iodine containing supplements[51]. Australian guidelines also recommend iodine supplementation and although 71% of the HCPs were aware of the recommendation, knowledge regarding the recommended dose and duration was low[52; 53]. Iodine supplements were recommended by 73% of the respondents during pregnancy, but only by ~50% in preconception and lactation. Reasons to not recommend supplements were the existence of fortification programs (28%) and lack of awareness of the recommendation (25%). The midwives who took part in the survey reported lack of knowledge (40%) and were less likely than the dietitians to discuss dietary sources of iodine, which only 40% of the HCPs reported discussing with women. In New Zealand, where public health nutrition has focused on iodine for several decades, almost 100% of healthcare workers (pharmacists, midwives and hospital nurses) reported a high knowledge of iodine supplementation and fortification (but the sample of this survey was smaller (n=25) compared to the rest of the surveys)[54]. Knowledge has been also associated with the speciality of the HCPs in Turkey. Endocrinologists had significantly higher knowledge and awareness on iodine supplementation, duration, and iodised salt compared to family practitioners and obstetricians. However, in the same survey, knowledge was very low for all three specialities (endocrinologists, family practitioners and obstetricians) when asked whether supplementation in pregnancy should be recommended during the existence of food and salt iodisation programs[55].

In the UK, only 46% of midwives could correctly identify seafood as a source of iodine, and 23% dairy products[56] – this is not surprising since nutrition is still not a significant part of the curriculum. Most midwives (67%) reported not mentioning iodine in antenatal care, as only 20% could link it to fetal development and 10% were aware of the increased iodine requirements during pregnancy. A need and strong interest for further education on iodine was expressed by the majority of HCPs interviewed, focussing on pregnancy, guidelines and sources[57; 52; 53].

Women of childbearing age

Globally, both iodine knowledge and awareness are low among women of childbearing age (pregnant, lactating or not). In a cross-sectional survey of 1026 UK mothers, 55% were unable to identify sources of iodine, commonly mistaking salt (21%) and vegetables (54%) as iodine-rich foods. However, most (87%) reported willingness to modify dietary behaviour if they received information related to the importance of iodine in pregnancy. In this study, only 9% of women surveyed could recognise milk as a source of the micronutrient[18]. Similar were our findings from the interviews of 48 women in pre-conception, pregnancy and new mothers. Women reported rarely discussing iodine with their HCPs, and lacking knowledge of dietary sources and importance of iodine for the fetal development

[43]. In Australia, a country with mild iodine insufficiency in pregnancy and mandatory iodine fortification of salt and bread as well as recommendations for iodine supplementation in pregnancy, knowledge regarding the adverse outcomes of ID and the importance of iodine has been found to be consistently poor in pregnant women[58; 59; 52; 60; 61]. Low self-confidence on whether women met the iodine requirements (20%) could be explained from the lack of knowledge of dietary sources of iodine. Seafood, the most commonly recognised iodine source, was correctly identified by 23-55% of the women, depending on the survey. However, milk was only recognised as a rich source of iodine by 15-29% of pregnant women. Almost half of pregnant women mistook vegetables as rich sources of iodine. Finally, supplementation with iodine was not considered necessary by 41% of pregnant women, dropping to 18.5% when they followed a diet perceived to be "healthy". Knowledge was identified as a predictor of iodine supplementation, and women who thought that the intake of iodine supplements in pregnancy is important, regardless how healthy a diet they follow, were more likely to take supplements containing iodine[60]. Poor knowledge did not improve after introduction of the mandatory iodine fortification program[62]. In Iran, similarly, women of childbearing age have low knowledge, awareness and practice in relation to ID [63; 64; 65], which has been linked to lower iodine status[66]. As a result, increasing awareness and knowledge would be potentially a cost-effective way of increasing iodine intake.

Global prophylactic measures and the UK

The potential level of intellectual impairment in a significant proportion of the population, and the net cost to both society and the economy due to iodine insufficiency are important. An iodine insufficient population poses high healthcare and societal national costs - with iodine supplementation in pregnancy modelled to save £199 in healthcare costs and £4476 from a societal perspective (for an increase of 1.22 IQ points per offspring)[67]. To date, there is no public health nutrition program in the UK addressing this pressing, totally preventable, concern, such as fortification or supplementation. Moreover, dietary recommendations for iodine have not changed since 1991.

Iodine Recommendations

The World Health Organisation (WHO) / United Nations Children's Fund (UNICEF) / International Council for the Control of ID Disorders (ICCIDD) recommended daily intake for adults is 150 µg/day, increasing to 250 µg/day for pregnant women[3]. The European Food Safety Authority (EFSA) proposed in 2014 a new reference value of adequate intake for pregnant women of 200 µg/day[68]. The United State Institute of Medicine (IoM) and the Food Standards Australia New Zealand (FSANZ) also propose an increase in iodine intake for pregnancy and lactation. However, in the UK, the Department of Health Reference Nutrient Intake (RNI) is for adults 140 µg/day, with no proposed increment for pregnancy and lactation (Table 2)[69]. Iodine requirements vary with age (Table 2), with no gender differentiations in the recommendation, beside from pregnancy and lactation. However, it is now recognised that iodine intake in pre-conception is important and may impact on neonatal outcomes[70].

There is an ongoing debate regarding the thresholds of sufficiency in pregnancy and the different existing recommendations for TUL of intake, which ranges from 600 μg/day [71] in Europe (Scientific Committee on Food) to 1,100 μg/day [72] in the US (Institute of Medicine). A large-scale cross-sectional study in Chinese pregnant women suggested that urinary iodine concentration (UIC) in pregnant women should not exceed 250 μg/l in iodine sufficient regions, due to high risk of subclinical hypothyroidism (1.75-fold increase in UIC 250-500 μg/l. UIC exceeding 500 μg/l is also associated with isolated hypothyroxinaemia (2.85-fold increase). Levels of autoimmunity, following a U-shape curve, are lowest in women with UIC 150-250 μg/l. This leaves a potentially narrow margin of sufficient intake, which would be difficult to control around the world, due to the different iodine content of foods, salt and lack of labelling[73]. Accordingly, Lee and Pearce [74] proposed that the upper level of sufficiency in pregnancy should be an intake of 250 μg/day.

Since 15-20 mg of iodine is stored in the body of a healthy adult (70-80% in the thyroid), intermittent consumption is acceptable, with thyroid hormone synthesis requiring approximately 60-95 μg of iodine per day based on iodine turnover, which is close to the lower reference nutrient intake (LRNI) of 70 μg/day [75]. The recommended WHO intake of 250 μg/day could be met by consuming two portions of fish per week, and dairy to the equivalent of two glasses of milk (drinks, in cereals), plus one yoghurt and a cheese serving per day. However, many women avoid these foods and lack guidance on how to include them in their diet.

Universal salt iodisation and fortified foods as potential vehicles

The elimination of ID and related disorders is a priority for the WHO and UNICEF. Universal salt iodisation has been adopted by over 120 countries globally[16]. It is the main method of iodine prophylaxis worldwide, firstly proposed in 1820. First attempt of salt fortification with iodine was done 100 years later[16]. The proposed iodisation of salt is 20-40 mg/kg and is based on an average salt intake of 10g daily. Salt has been chosen as a vehicle of salt iodisation as it combines characteristics that make it suitable, including its stable consumption throughout the year, low cost, consumption by everyone in a population, ease in implementation, quality, odour and taste not being affected and monitoring of production and[76].

Salt iodisation is not considered unanimously a good practice for the control of ID and there is still a debate on its success and potential risks, which might contribute to the lack of legislation for salt fortification in the UK. The perceived conflicting messages that universal salt iodisation would convey remains at odds with public health campaign for salt reduction to less than 5 g/day[(77; 78)]. Experts from the WHO, UNICEF and ICCIDD work together to overcome any counterproductive effects of the two public health campaigns and find a common ground for their parallel success[(79)]. According to the WHO, salt iodisation and salt intake reduction (in less than 5 g/day), are both important and there is a need to understand that they can be compatible[(80)]. Iodine fortification could increase in line with the decrease of salt intake and mandatory fortification would remove the positive bias of iodised salt as "healthier"[(79)]. Further argument need to be considered, including (lack of) freedom of choice in the context of mandatory fortification and the risk of high exposure / toxicity for a sub-group of the population.

While IDD have been successfully eliminated or controlled in many countries, via salt fortification in combination with diet diversification (in the US[(81)] and Ghana[(82)], with exceptions in European countries[(83)]), consumption of fortified salt may not be a sufficient measure in pregnancy[(84)]. Studies in Italy[(85)], Turkey[(86; 87)] and Tasmania[(88)] showed that ID in pregnant women persisted even after the application of universal salt iodisation, with UIC<150 μg/l in 92%, 50-78% and 73% of pregnant women in each country respectively. Salt fortification with iodine is voluntary in the UK; iodised salt therefore does not contribute to the iodine intake of the population, with restricted availability in the market (weighed availability in marketshare 21.5%)[(89)].

Fortification of other foods is also an option, although the ICCIDD does not support individual food iodisation[(90)]. In Bangladesh and Pakistan, fortification of processed foods with iodised salt increased the availability of iodine in the population, and manufacturers use it when legislation permits that, as it does not negatively affect the food characteristics[(91)]. Fortification of bread with iodised salt, in Australia, resulted in increased iodine intake in pregnancy (median UIC 124.2 μg/day, IQR 121.1-127.2) and postpartum (median UIC 123.4 μg/day, IQR 119.7-127.1)[(92)]. The choice of bread was the result of extended modelling for the identification of be the best vehicle for the increase of iodine intake[(90)]. Recently, biofortification of vegetables with iodine was also proposed as an opportunity to increase iodine intake. Positive results have been published after the consumption of fortified vegetables in 50 healthy volunteers in Italy, with UIC increased by 19.6% ($p<0.05$)[(77)]. Turmeric can also help in the elimination of goitre in increase of iodine intake, based on a study in Pakistan. The authors of this study suggest that the use of iodine fortified salt should not be overemphasised, as alternatives (such as turmeric) could be implemented[93], an opinion which is not widely accepted considering the usefulness of iodised salt in the correction of IDD[94] .

A meta-analysis of nine RCTs (1990-2012) looked at the effect of iodine-fortified foods on UIC of children aged 7-10.5 years. Fortified foods included biscuits, meals and milk and the contained dose of iodine ranged from 25 to 200 μg/l, consumed for 4-30 months. At baseline, the UIC was similar in both intervention and controlled groups (heterogeneity Q=942.47, df=13). No carry-over effect was observed in cross-over trials, so trials with both cross-over and parallel designs were included in the meta-analysis. The standard mean UIC was significantly higher in the fortified group when compared to the control group (SMD= 2.02, $p<0.001$) with iodine fortified foods effective to improve UIC in children[95].

The acceptance on biofortified foods predisposes examining attitudes of the population towards them. Based on the Protection Motivation Theory, parents and school heads in Uganda were surveyed regarding their reactions to adopting iodine biofortified staple foods in the school feeding programs. Knowledge of parents and school heads about micronutrients, IDD and biofortification was low, with iodine and salt iodisation being the only two topics with higher awareness. On the other hand, threat appraisal (perceived severity, vulnerability and fear to evaluate ID) and coping appraisal (response efficacy, cost response and self-efficacy to deal with ID through biofortified foods) were high for both sub-samples, which favours the protection motivation. The intention to adopt biofortified legumes was high and depended on factors including cost of the products, age and gender of the respondents. Key aims of a feeding program should include increased awareness of the health effects of ID and low cost of the biofortified foods[96].

Supplementation in pregnancy

Supplementation is an alternative strategy to address iodine insufficiency in pregnant and lactating women. However, Healthy Start supplements, provided by the UK health services do not contain iodine, and commercial alternative are expensive. Similarly to the US[81], marketed pregnancy supplements are not required to contain iodine, although their use has been associated with a 40% higher urinary iodine concentration in Spanish pregnant women[97]. The American Thyroid Association, the Endocrine Society and the US National Academy of Sciences have proposed that all prenatal supplements should include 150 μg of potassium iodide[81]. The WHO also recommends iodine supplementation in pregnancy and lactation in all countries where iodised salt is available in less than 20% of the households[3].

A recent Cochrane review of positive and negative health effects of iodine supplementation in preconception, pregnancy and lactation, for the mother, the infant and the child highlighted inconclusive evidence [98]. There was indication of both of harm and of benefit in places of mild to moderate deficiency. The number of available studies was limited, potentially due to the ethical difficulties implementing studies with a placebo / control group in pregnancy. Potential benefits included lower likelihood of insufficient iodine status in pregnancy, congenital abnormalities, postpartum hyperthyroidism, neonatal goiter and neonatal insufficient iodine intake[98]. Potential harm included overactive thyroid function, nausea and vomiting during pregnancy. A cohort study in pregnant women with mild to moderate ID, including women receiving prenatal iodised (150μg) supplements (n=168), women who regularly used iodised salt (n=105) and a control group of women (n=160), found that TSH was significantly higher in women taking supplements than in the other two groups, and 26% of women had higher TSH than the upper limit for gestation. Consequently, as mild ID women that take daily a 200 μg iodine supplement from the beginning of their pregnancy might have an increased TSH and risk of maternal hyperthyrotrophinaemia, supplementation with iodine for a long period prior to conception is suggested for women living in mild to moderate deficient areas[99]. Iodine supplementation did not have an effect on thyroid dysfunction in a mild to moderate deficient area in Denmark, in thyroid peroxidase antibody (TPO-Ab) positive pregnant women. Women who participated in a placebo control RCT, received a daily mineral and vitamin tablet with or without 150μg iodine (no iodine, iodine during pregnancy only, iodine during pregnancy and postpartum) and postpartum thyroid dysfunction developed in 55% of the participants, without any difference between the three groups[100].

Beside impact on iodine status and thyroid function, the effect of iodine (supplementation) on neurodevelopment is critical and should be the key outcome for assessment of supplementation efficacy. Iodine intervention studies in pregnancy have measured an actual cognitive outcome in children from 3 months to 5.4 years [101; 102; 103; 104; 105; 106; 107; 108; 109]. In India and Thailand , iodine supplementation in pregnancy did not lead to a measurable difference in verbal IQ, performance IQ or the global executive composite (GEC) score from the Behaviour Rating Inventory of Executive Function Preschool Version (BRIEF-P), assessed in children at 5.4 years (200 μg daily iodine or placebo during pregnancy)[109]. The Spanish multicentre mother-and-child cohort (INMA cohort, Valencia, Sabadell, Asturias and Gipuzkoa areas) in 1519 1-year-old infants showed a lower Psychomotor Development Index (PDI) score (- 4.9 and -5.5 points respectively) in children whose mothers were taking ≥150 μg/day from supplements compared to children whose mothers consumed <100 μg/day iodine from supplements (Bayley scales of Infant Development for psychomotor and cognitive development) in the regions of Asturias and Valencia. When the results of all the areas were put together for the comparison of these two groups (≥150 μg/day versus <100 μg/day from supplements) a 1.5-fold increase in the odds of a PS score less than 85 was found (which might indicate a slight delay in neuropsychological development) but no difference for the Mental development index or UIC[106; 107]. Furthermore, no significant differences in children's neurological development were shown is iodine supplementation studies in pregnant women in Spain [108] and Australia[110] . However, the Australian study stopped without recruiting the required number of participants and results may be underpowered. A key factor in the interpretation of these studies is the age of assessment, since neurocognitive testing is not reliable in the youngest groups.

Severe ID, mainly in early pregnancy, was shown to lead to cretinism in a trial of iodine supplementation through intramuscular injection[102]. Positive associations between supplementation in mild-to-moderate deficient areas and children's neurodevelopment was shown in Spain. Daily potassium iodide supplement (300 μg/day) in first trimester led to an increased PDI score in children (assessed at age 3-18 months) [105]. Positive results of iodine supplementation in pregnancy (200 μg KI/day) in relation to neurodevelopment have been also found in a study in 18-month-old children born to women with hypothyroxinemia in early pregnancy[104]. Finally, IQ score was 11.2 points higher (95% CI, 7.96- 14.46) in 4-23 months old children of women that received iodine via intramuscular injection during pregnancy (after the prenatal consultation between 20 and 36 weeks of gestation) or delivery; however, those studies were published 40-50 years ago, in areas with severe iodine deficiency and endemic goiter[101; 103].

From those intervention studies, there is overall a neutral or positive impact of supplementation during pregnancy on neurological development of the infant. However, the reliability of the different assessment methods of neurodevelopment in a very early age might be a potential reason for the non-conclusive results. More well-designed and longer-term studies are needed to draw conclusions, assessing neurological development in older children[111].

Considerations for the future

The re-emergence of ID in the UK, highlighted in 2011[12], is not a new public health concern anymore - however 60% of pregnant women still have an iodine intake lower than the WHO recommendation[18]. Eating patterns have changed in the last 20 years, with a decrease in milk intake[40], potentially driven by commercial pressures and marketing (e.g. promotion of milk alternatives). Simultaneously, changes have occurred in farming practices, due to thyrotoxicosis from the high levels of iodine in milk as a result of the addition of iodine in cattle feed and use of iodophor disinfectants used in sanitisation[112; 113]. The consequences of ID are not limited to the periconception and pregnancy periods, since the effects of ID are often lifelong and irreversible, thereby impacting on society, with decreased productivity and increase costs[67]. Prophylaxis via salt fortification is relatively cheap (2-7 US cents/kg, <5% of salt retail price)[114] but may not be a sufficient measure during pregnancy and lactation. Meanwhile, evidence of the benefits of supplementation is still unclear, and potential impacts on recommendations made by HCPs.

ID is a diet-related challenge, and the strategy to tackle this challenge must include public health and policy strategies, without ignoring the role of foods, dietary recommendation, and knowledge / awareness. The lack of involvement of diet and nutrition professionals as part of the solution, and the lacking nutrition content of most curriculum for the health profession are likely blunt the effectiveness of any given strategy and should be re-evaluated. Iodine-rich sources in the diet are varied and our qualitative study has shown that women of childbearing age are receptive to dietary and lifestyle changes as long as guidance and support is provided, inviting strategies in this area. However, dietary guidance during antenatal care is perceived to be insufficient and confusing, driving women to use other sources of information, sometime less credible[43]. A clear need for empowerment in pregnancy emerges, as women are willing to follow specific and comprehensive dietary advice in pregnancy. Public Health strategies and educative programs could therefore influence the improvement of nutritional status in the perinatal period and increase of iodine status of the population.

There is very limited evidence on the effectiveness of educative programs and food-based interventions in increasing iodine intake and improving iodine status of pregnant women, as studies tend to focus on the success, harm and benefits of supplementation and salt fortification. Our systematic review of the literature from 1990 to 2016 identified a lack of intervention studies focusing on foods (rather than supplements and fortification) or educative programs to increase iodine intake in pregnancy[115]. Of the three studies that met the inclusion criteria, one was a proposed study protocol[116], another (LIMIT study, South Australia) was an intervention in overweight and obese women, at 10-12 weeks of gestation without specific focus on iodine[117], and the third was a randomised controlled trial (Tehran, Iran) of pregnant women, between the 4th and 18th weeks of pregnancy[118]. The RCT, the only piece of evidence directly linked to iodine, concluded that the intervention (a 4-months educational program using face-to-face educational sessions, a leaflet in the second and the third trimesters, as well as telephone) increased knowledge, attitude and practice, but not iodine status. Iodine status was however reported as median UIC of the groups, measured from a single spot urine sample, and may not be the most appropriate tool to evaluate changes in status in this small group. Randomised controlled trials are urgently needed to examine the effectiveness of different approaches as well as the long-term health, neurocognitive and economic effects on the population. Including food guidance as a dimension of any future intervention is a vital step before the implementation of policy and public health campaigns, which would also be socially and politically acceptable. The UK offers a great opportunity for further research, as it is an ideal terrain for interventions, lacking prophylaxis such as salt fortification and supplementation.

ID has been described as “the low-hanging fruit of public health” in the UK[119]. The challenge could be tackled through a range of strategies, including policy implementation (salt and staple foods iodisation, supplementation), educational campaigns for increased awareness in women and HCPs, and development of comprehensive food-based guidance for the general population, pregnancy and lactation. However, none of those potential solutions is in place now in the UK, and the problem of insufficiency has been consistently overlooked. Recently, the Scientific Advisory Committee on Nutrition (SACN) published an updated report on iodine, with no recommendations to revise the reference intake values[120], indicating that the existing evidence might not be sufficient for a policy revision. Governmental actions are required, and the UK should follow the example of other countries, such as the US, Australia and New Zealand in policy for fortification and supplementation according to the WHO[16]. The cases of cessation of water fluoridation (in Scotland) and absence of mandatory fortification for folate are two similar examples of potential missed-opportunities to positively impact on population health, possibly through a more rigid policy-making framework compared to other Western nations. In less developed countries, focus on an increased household coverage with iodised salt, and addition of iodine to condiments, soybean paste and sauce is driven by the Iodine Global Network / ICCIDD strategy on global elimination of iodine deficiency[121; 122]. Co-existing deficiencies, such as iron, zinc and selenium should also be taken into consideration[123], as they are important for thyroid function, improvement of the efficacy of iodine supplementation, and prevention of myxedematous cretinism[124]. The WHO is targeting micronutrient deficiencies globally by proposing a balanced and diversified diet, micronutrient supplementation and fortification of foods (i.e. sugar, salt, maize, oil, rice, wheat) with micronutrients (folic acid, iron, calcium, vitamin A, B12, zinc)[123].

To address ID effectively, solutions should work synergistically. Changing dietary patterns is challenging, considering the unregulated commercial marketing of foods. The example of fruits and vegetables provides the evidence that dietary changes can happen, and interventions designed to increase a dietary component can be successful, although slow. Dietary change is however mostly effective in subgroups of the populations, leaving the lower socioeconomic groups and those with the greatest need (e.g. low income, homeless, socially deprived, urban migrant groups) untargeted[125;

[126]. This in itself calls for a multipronged approach to tackle ID, in the UK and globally, depending on the needs and iodine status of each population.

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Conflict of Interest

None.

Authorship

M. B. gathered and critically appraised the literature and drafted the manuscript. E. C. and M. E. J. L. reviewed and contributed to the manuscript.

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Tables and Figures

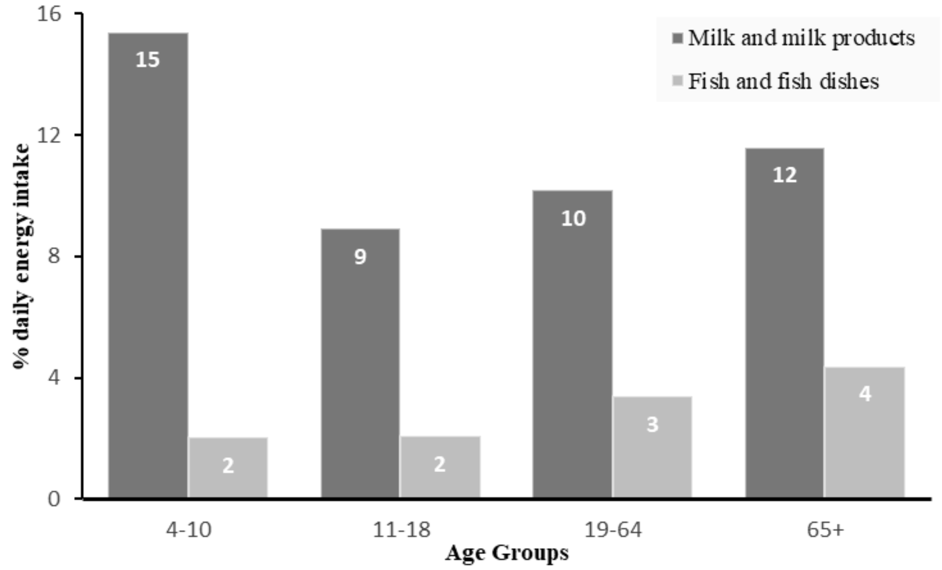

Figure 1 Iodine-rich foods percentage contribution to daily average total energy intake in women in the UK, based on their age group, based on the NDNS Rolling program (Years 5-6)[15].

Table 1 Epidemiological criteria for assessing iodine nutrition in a population based on median and/or range of urinary iodine concentrations[3].

	Median urinary iodine (µg/l)	**Iodine intake**	**Iodine nutrition**
School children	<20	Insufficient	Severe iodine deficiency
	20-49	Insufficient	Moderate iodine deficiency
	50-99	Insufficient	Mild iodine deficiency
	100-199	Adequate	Optimal
	200-299	Above requirements	Likely to provide adequate intake for pregnant/lactating women, but may pose a slight risk in the overall population
	>300	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)
Pregnancy	<150	Insufficient	
	150-249	Adequate	
	250-499	More than adequate	
	≥500	Excessive	
Lactating women	<100	Insufficient	
	≥100	Adequate	

Children < 2 years old	<100	Insufficient
	≥100	Adequate

Table 2 Existing iodine recommendations (µg/day)

	FAO/WHO (2004)	**EFSA (2014)**	**US IoM (2001)**	**FSANZ (2006)**	**UK DoH (1991)**
Preschool children (0-59 months)	90	70-90	90	90	60-70
Schoolchildren (6-12 years)	120	90-120	90-120	90-120	100-130
Adolescents (>12 years) / Adults	150	150	150	150	140
Pregnancy	250	200	220	220	140
Lactation	250	200	290	270	140