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The impact of iodised salt or iodine supplements on iodine status during pregnancy, lactation and infancy

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Abstract

Objectives: Monitoring of iodine status during pregnancy, lactation and infancy is difficult as there are no established reference criteria for urinary iodine concentration (UI) for these groups; so it is uncertain whether iodized salt programs meet the needs of these life stages.
Design and Subjects: The method used in this paper was: 1) to estimate the median UI concentration that reflects adequate iodine intake during these life stages; and 2) to use these estimates in a review of the literature to assess whether salt iodisation can control iodine deficiency in pregnant and lactating women, and their infants.
Results: For pregnancy, recommended mean daily iodine intakes of 220-250 μg were estimated to correspond to a median UI concentration of about 150 $\mu g\,l^{-1}$, and larger surveys from the iodine sufficient countries have reported a median UI in pregnant women $\geq 140\ \mu g\,l^{-1}$. Iodine supplementation in pregnant women who are mild-to-moderately iodine deficient is beneficial, but there is no clear affect on maternal or newborn thyroid hormone levels. In countries where the iodine intake is sufficient, most mothers have median breast milk iodine concentration (BMIC) greater than the concentration (100-120 $\mu g\,l^{-1}$) required to meet an infant's needs. The median UI concentration during infancy that indicates optimal iodine nutrition is estimated to be $\geq 100\ \mu g\,l^{-1}$. In iodine-sufficient countries, the median UI concentration in infants ranges from 90-170 $\mu g\,l^{-1}$, suggesting adequate iodine intake in infancy.
Conclusions: These findings suggest pregnant and lactating women and their infants in countries with successful sustained iodised salt programs have adequate iodine status.

Keywords
Iodine
Pregnancy
Lactation
Urinary iodine
Breast milk iodine

Introduction

Iodine deficiency (ID) causes a broad range of adverse effects on health resulting from the inadequate production of thyroid hormone that are collectively termed ID disorders (IDD). An ID during pregnancy increases the risk of spontaneous abortion, low birth weight and infant mortality[1–5] as well as raising the risk of neuromotor, behavioural and cognitive impairment in the offspring[6–8]. Even a mild-to-moderate ID during pregnancy can cause transient hypothyroidism, can increase the thyroid volume in mothers and their infants, and may impair cognition[9–13]. During infancy, an adequate amount of iodine is required for normal mental development[12,13]; a meta-analysis estimated that ID in a population lowered mean IQ scores by 13.5 points[14]. It is for these reasons that IDD control programmes should focus on pregnancy, lactation and infancy, the stages in life when iodine requirements are at their greatest.

However, the assessment of iodine status during these life stages is challenging. The main indicator in a population of a response to salt iodisation is the median urinary iodine (UI) concentration[15], but there are no established reference values for the median UI concentration during pregnancy, lactation or infancy. A median concentration of iodine in the range of 100–199 $\mu g\,l^{-1}$ in the urine of school-aged children and in non-pregnant, non-lactating adults indicates an adequate iodine intake and optimal iodine nutrition[15]. This range has not been validated to reflect an adequate iodine status in pregnant and lactating women or in infants and, as discussed below, if applied to these target groups is likely to underestimate the true degree of ID. Most large systematic surveys of ID have been done in school-aged children or in the general adult population, and have only rarely included pregnant or lactating women, or infants. Many of the studies on pregnant women and infants have comprised only small numbers, and sampling has rarely been representative, making it difficult to draw firm conclusions. Despite this, there is some concern over whether iodised salt programmes meet the needs of these life stages. Therefore, the general objectives of this paper are to:

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1. Review the current recommended iodine intake in pregnancy, lactation and infancy.
2. Estimate the median UI concentration that reflects an adequate iodine intake during these life stages.
3. Use the estimates of an adequate UI concentration to assess whether current approaches to salt iodisation and iodine supplementation can control ID in pregnant and lactating women, and in their infants.

Methods used to estimate the requirement for iodine

There are three main ways of estimating how much iodine is required to meet daily needs.

Iodine turnover

The daily uptake and turnover of radioactive iodine can be used to estimate the requirement for iodine, provided that the subjects being tested have an adequate iodine status and are euthyroid[16–18].

Iodine balance

Several studies have estimated iodine requirements from balance experiments[19–23], but they have serious limitations. This is mainly because many ingested substances contain unrecognised iodine, so that a strict control of iodine intake is difficult to achieve. Because of the need to consider the iodine content of the thyroid gland, in addition to iodine intake and excretion, even during prolonged balance studies, an equilibrium may not clearly be established[19].

Urinary iodine concentration and thyroid size

Since >90% of dietary iodine eventually appears in the urine[23,24], the concentration of iodine in urine is an excellent indicator of recent iodine intake. An increase in thyroid size is the earliest clinical sign of impaired iodine nutrition and reflects an adaptation to the threat of hypothyroidism.

Definitions of recommendations for iodine intake

The United States Institute of Medicine (IOM) has proposed several categories of reference intake[25]. The recommended dietary allowance (RDA) is the average daily iodine intake sufficient to meet the iodine requirement of about 97% of healthy individuals in a particular life stage. It is intended to be used as a goal for the daily intake of iodine by individuals.

The RDA is based on the estimated average requirement (EAR) which is the daily iodine intake, defined by specific criteria, that meets the requirement of half of the healthy individuals in a particular life stage. It assumes a normal distribution of intake. The RDA is derived from the EAR after taking into consideration the estimated variability in individual requirements. The EAR is not meant to be used to define the intake of individuals, but can be used for groups.

The adequate intake (AI) can be given if there is not enough scientific evidence to calculate an EAR. For example, the AI of iodine during infancy is based on observed mean iodine intakes by healthy, full-term, breast-fed infants in areas where iodine intake is known to be sufficient. The AI is expected to meet or exceed the amount of iodine needed in almost all individuals in the specified population group, and can be used as a goal for individual intake.

According to the WHO, UNICEF and the ICCIDD, the recommended iodine intake is the amount estimated to cover the needs of nearly all healthy individuals in the specified life stage[15].

Iodine requirements

Non-pregnant women

Studies of iodine turnover, radioiodine uptake by the thyroid and balance studies of euthyroid adults have suggested that the average daily requirement for iodine is 91–96 μg per day[16,17,20]. There is no evidence to suggest that the average iodine requirement of adults varies with age[25]. Thus, the IOM have set the EAR of iodine by women $\geq$14 years at 95 μg per day[25]. The RDA, which is defined as the EAR plus twice the coefficient of variation of intake of the population and then rounded to the nearest 50 μg, is 150 μg day^{-1} for females $\geq$14 years[25]. This amount agrees with the WHO, UNICEF and the ICCIDD recommended daily iodine intake for non-pregnant women of 150 μg per day[15]. These amounts are summarised in Table 1.

Pregnant women

The iodine requirement during pregnancy increases for three reasons: (1) an increase in the production of thyroxine (T_4) by the mother to maintain her euthyroid state and transfer thyroid hormone to the foetus; (2) the transfer of iodine to the foetus, particularly in late gestation and (3) an increase in renal iodine clearance (RIC) by the mother[26,27]. The amount of iodine accumulated by the infant at the time of delivery has been used to estimate the daily foetal iodine uptake. The average iodine content of the thyroid gland of a newborn is 50–100 μg, with >95% daily iodine turnover[28,29]. Balance studies have found that the average iodine retention of full-term infants is 6.7 μg kg^{-1} per day[30], so the mean retention of iodine by a healthy foetus with a weight of 3 kg would be about 22 μg day^{-1}. An estimated daily iodine uptake by the thyroid gland of about 75 μg day^{-1} by the foetus and an EAR of 95 μg day^{-1} for non-pregnant women would yield an EAR of 170 μg day^{-1} during pregnancy. The balance studies of Delange *et al.* suggest an EAR of $22 + 95 = 117$ μg per day[30]. Dworkin *et al.* found that five pregnant women were in iodine balance when

Table 1 The intake of iodine by women of child-bearing age, pregnant and lactating women, and infants recommended by the WHO, UNICEF and the ICCIDD[15] and by the United States Institute of Medicine[25].

Authority	Life stage	Basis of amount	$\mu g\,day^{-1}$
WHO, UNICEF, ICCIDD	Children 0–59 months		90
	Women >12 years		150
	Pregnant and lactating women		200
United States Institute of Medicine	Infants 0–6 months	AI	110
	Infants 7–12 months	AI	130
	Women ≥14 years	EAR	95
	Women ≥14 years	RDA	150
	Pregnancy	EAR	160
	Pregnancy	RDA	220
	Lactation	EAR	209
	Lactation	RDA	290

AI, adequate intake; EAR, estimated average requirement; RDA, recommended daily allowance.

consuming about 160 $\mu g\,day^{-1}$, with no significant differences pre- and post-partum[19]. Several authors have measured the thyroid volume during pregnancy and correlated it with the UI concentration and the effects of iodine supplements. In the studies of Romano *et al.*[31] and Pedersen *et al.*[9], total daily iodine intakes of about 200 and 250–280 μg, respectively, during pregnancy prevented an increase in thyroid volume, while in the study of Glinoer[10], a total daily iodine intake of about 150 μg was insufficient to prevent an increase in thyroid size. On the basis of these data, the IOM set the EAR at 160 $\mu g\,day^{-1}$ for pregnancy in women ≥14 years, and set the RDA, estimated to be 140% of the EAR rounded to the nearest 10 μg, at 220 μg per day[25]. The WHO, UNICEF and the ICCIDD recommend a daily iodine intake of 200 $\mu g\,day^{-1}$ for pregnant women, a value 10% lower than the RDA[15] (see Table 1).

Lactating women

If a lactating woman produces an average of 0.78 and 0.60 l of milk per day during the first and second 6 months of infancy, respectively[25], and if the mean breast milk iodine concentration (BMIC) is 146 $\mu g\,l^{-1}$ in iodine-sufficient women in the USA, the average daily loss of iodine in breast milk has been estimated to be about 114 μg per day[25]. When this amount is added to the EAR of non-pregnant women of 95 $\mu g\,day^{-1}$, the EAR for lactating women ≥14 years is estimated by the IOM to be 209 μg per day[25]. The RDA is thus 140% of the EAR rounded to the nearest 10 μg, which is 290 $\mu g\,day^{-1}$ of iodine. The WHO, UNICEF and the ICCIDD recommend a daily iodine intake of 200 $\mu g\,day^{-1}$ by lactating women[15], which is similar to the EAR but 30% lower than the RDA (see Table 1).

Infancy (0–12 months)

Since no functional criteria are available that reflect iodine intake in infants, recommended intakes are based on the mean iodine intake of healthy full-term infants fed on human milk. The IOM based their recommendation on the median BMIC of women in the United States of America (USA) in the early 1980s, which was 146 μg per l[25]. Since the iodine intake of the population of the USA was relatively high at this time[32], this BMIC is at the upper end of the range of 78–167 $\mu g\,l^{-1}$ reported for women in iodine-sufficient countries (see later discussion). Based on estimates of the mean daily volume of breast milk, the mean amount of iodine secreted in human milk is estimated to be about 115 μg per day[25]. Balance studies of full-term infants given 20 $\mu g\,kg^{-1}\,day^{-1}$ of iodine found that the total amount excreted was 12.7 $\mu g\,kg^{-1}\,day^{-1}$ and the amount retained was 7.3 $\mu g\,kg^{-1}$ per day[30]. If the reference body weight of an infant aged 6 months is 7 kg[25], the daily amount of iodine excreted by an infant in positive balance is 90 μg. Considering these data, the recommended AI of iodine for infants aged 0–6 and 6–12 months has been set at 110 and 130 $\mu g\,day^{-1}$, respectively, by the IOM[25]. The WHO, UNICEF and the ICCIDD recommend a daily iodine intake of 90 $\mu g\,day^{-1}$ for infants[15], which is 20–30% lower than the RDA (see Table 1).

Iodine intakes in pregnancy and the effects of iodine supplementation

Pregnancy

The WHO, UNICEF and the ICCIDD recommend using the median UI concentration to assess the iodine nutrition of populations[15]. The daily iodine intake can be extrapolated from the UI if it is assumed that girls aged 7–15 years produce 0.9 ml urine h^{-1} per kg[33], and adult women produce about 1.5 l per day[34]. If it is assumed that the mean bioavailability of iodine is 92%, the recommended daily iodine intakes during pregnancy of 200[15] and 220 μg[25] would correspond to a UI concentration of 120–135 $\mu g\,l^{-1}$ in pregnancy. As pregnancy may occur in adolescence, particularly in developing countries, a 15-year-old girl weighing some 50 kg with a daily iodine intake of 200 or 220 μg would have a UI concentration of 170–190 $\mu g\,l^{-1}$.

However, during pregnancy, it may be less valid to estimate the iodine intake from the UI concentration due to an increase in the glomerular filtration rate[35] and,

possibly, an increase in RIC[36]. If the RIC increases during pregnancy, the daily iodine intake extrapolated from the UI concentration in pregnancy would be lower than that in non-pregnancy. However, the evidence for an increase in RIC and a consequent decrease in the plasma inorganic iodide (PII) concentration during pregnancy is equivocal. The study of Aboul-Khair *et al.* suggested an increase in RIC using an indirect method[36], while Liberman *et al.* directly measured the PII concentration and reported no significant difference in PII or UI concentration both pre- and post-partum in 16 women living in a population with a high iodine intake[37]. The iodine balance study of Dworkin *et al.* also found no differences in the UI concentration both pre- and post-partum[19]. Owing to the lack of clear data, it is uncertain whether pregnancy *per se* significantly increases the UI concentration. Therefore, in this review, the above extrapolations from UI concentration to daily iodine intake proposed by the IOM[25] were considered valid, and the recommended daily intakes of 200–220 μg of iodine[15,25] were considered to correspond to a median UI concentration of 125–135 $\mu g\,l^{-1}$ in adult pregnant women, although a higher median of about 170–180 $\mu g\,l^{-1}$ may be more appropriate if pregnancy occurs in early adolescence. Although more data are clearly needed, a median UI concentration in pregnant women $\geq 140\ \mu g\,l^{-1}$ has been used in this review as an indicator of adequate iodine intake.

Table 2 compares the UI concentration of pregnant women with the general population in countries with iodine intakes ranging from excessive to deficient. Most studies analysed spot urine samples and few had an adequate power to classify iodine status based on a median UI concentration from such samples[38]. Few studies have compared the UI concentration of pregnant women with a control group of non-pregnant women. As shown in Table 2, the UI concentration in pregnant women and in the general population generally appear to be similar. However, this may be due to a preponderance of studies in areas where there is low or marginal iodine sufficiency, as several studies in iodine-sufficient countries have found a significantly higher median UI concentration in pregnant women[39–43]. All of the large studies in iodine-sufficient countries have reported a median UI concentration in pregnant women of $\geq 140\ \mu g\,l^{-1}$. This includes countries where all salt is iodised (Switzerland and Iran), and countries where dietary iodine comes from either iodised salt or from other food sources (USA, UK, Sri Lanka and Sweden). If a median UI concentration $\geq 140\ \mu g\,l^{-1}$ in pregnant women is taken to represent a mean iodine intake $\geq 200\ \mu g\,day^{-1}$, then it appears that the iodine status of pregnant women is adequate in countries where the general population is adequately covered either wholly or partially by iodised salt programmes.

Studies of thyroid size in pregnant women support these data. As shown in Table 3, in countries affected by mild or moderate ID (Ireland, Germany, Belgium, Italy and Denmark), the thyroid volume increases 15–31% during pregnancy, while in iodine-sufficient countries (Finland, USA and The Netherlands), there is little or no increase in thyroid volume during pregnancy[44]. This suggests that iodine status is adequate in pregnant women in iodine-sufficient countries with two important caveats. First, the question remains unanswered of whether RIC changes enough during pregnancy to confound the usual estimation of iodine intake based on the median UI concentration. Second, iodine-containing supplements taken during the prenatal period may have led to an increased median UI concentration in pregnant women living in countries with an iodised salt programme[45].

Iodine supplements during pregnancy and their impact on iodine status

In Europe, 13–50% of women receive iodine-containing supplements during pregnancy[45]. In a study of 511 pregnant Swiss women in 1999, although 70% received a prenatal supplement, only 13% received a supplement containing iodine; the median UI concentration in the women taking iodine-containing supplements was 194 vs. 130 $\mu g\,l^{-1}$ in non-supplemented women[42]. After a 33% increase in the concentration of iodine in salt, a study of 276 pregnant Swiss women in 2004 reported a median UI concentration of 254 $\mu g\,l^{-1}$; there was no significant difference in the median UI concentration of women taking iodine-containing supplements compared with those who were not[43].

In a recent study of 109 pregnant German women, the median UI concentration was 181 $\mu g\,g^{-1}$ creatinine (cr.); 58% were taking iodine-containing supplements and had a significantly higher UI concentration (204 $\mu g\,g^{-1}$ cr.) than women who were not (148 $\mu g\,g^{-1}$ cr.)[46].

In earlier studies of women in Denmark[47] and Germany[48], the median UI concentration was significantly higher in pregnant women supplemented with iodine than women not supplemented: 58 vs. 35 $\mu g\,day^{-1}$ in Denmark and 85 vs. 59 $\mu g\,day^{-1}$ in Germany.

In Hungary, about 50% of pregnant women receive a supplement containing iodine. In those women taking supplements containing $\geq 150\ \mu g$ iodine per day, the median UI concentration was 115–130 $\mu g\,g^{-1}$ cr., compared with 57–68 $\mu g\,g^{-1}$ cr. in women who were not supplemented[49].

In a cross-sectional study in Denmark, the use of iodine supplements of 150 $\mu g\,day^{-1}$ and thyroid function were assessed in 144 pregnant women and their newborns[50]. At full term, the median UI concentration of supplemented mothers was 60 $\mu g\,l^{-1}$ compared with 35 $\mu g\,l^{-1}$ in unsupplemented mothers. In the supplement group, the concentration of thyroglobulin (Tg) in both maternal and cord blood was significantly lower,

Table 2 Urinary iodine concentration[1–3] of pregnant women in longitudinal (L) and cross-sectional (C) studies and, if available, in the general population or in non-pregnant controls. The urinary iodine concentration in the post-partum period is shown if a longitudinal study continued after delivery.

Reference	Country	*n*	L or C	Trimester of pregnancy or time post-partum (PP)	Urinary iodine concentration	General population or controls
	Iodine excess					
37	Chile	19	L	1	594[1]	
		19	L	2	469[1]	
		19	L	3	786[1]	
		19	L	3 months PP	459[1]	
	Iodine sufficient					
67	Iran	403	C	1,2,3	186–338[2]	193–312[2]
40	Sri Lanka	–	C	1	181[2]	147[2]
			C	2	136[2]	
			C	3	154[2]	
68	Sweden	51	L	1	180[1]	
		51	L	2	170[1]	
		51	L	3	145[1]	
42	Switzerland	511	C	2, 3	138[2]	115[2]
69	Switzerland	153	C	1,2,3	205[3]	91[3]
43	Switzerland	281	C	1,2,3	254[2]	129[2]
40	UK	–	C	1	125[2]	73[2]
			C	2	170[2]	
			C	3	147[2]	
70	USA	290	C	1,2,3	148[1]	130[1]
11,41	Singapore	253	C	3	124[2]	98[2]
		230	L	1	107[2]	
				2	116[2]	
				3	124[2]	
				6 weeks PP	105[2]	
				3 months PP	104[2]	
	Iodine deficient					
71	Belgium	334	C	1,2	50[2]	50–75[1]
		334	C	2,3	45[2]	
		136	C	1	56[2]	
		133	C	2	50[2]	
		49	C	3	50[2]	
9	Denmark	26	L	2	51[2]	50[1]
		26	L	3	40[2]	
		26	L	1 week PP	30[2]	
		26	L	26 weeks PP	50[2]	
		26	L	52 weeks PP	58[2]	
72	France	306	L	1	50[2]	50–80[1]
		224	L	3	54[2]	
39,40	Ireland	38	L	1	135[2]	70[2]
		38	L	2	125[2]	
		38	L	3	122[2]	
53	Italy	67	C	1,2	74[3]	
31	Italy	18	C	3	50[1]	
54,73	Italy	10	L	1,2,3	33[1]	46[1]
51	Germany	70	L	1	55[3]	
		70	L	11 days PP	50[3]	
46	Germany	109	C	1,2,3	181[3]	
49	Hungary	119	C	1,2,3	57[3]	
74	New Zealand	35	L	1,2,3 and 3,6,12 months PP	24–52[1]	24–47[1]
75	Nepal	1021	C/L	1,2,3	96[1]	
		1028	C/L	13 weeks PP	61[1]	
76	Sudan	47	L	3	38[2]	76[2]
		47	L	3 months PP	51[2]	
		47	L	6 months PP	30[2]	
		47	L	9 months PP	63[2]	
77	Turkey	80	L	1,2,3	91[1]	85[1]

[1] $\mu g\,day^{-1}$; [2] $\mu g\,l^{-1}$; [3] $\mu g\,g^{-1}$ creatinine.

and the free T_4 concentration was significantly higher, than in unsupplemented women[44]. Although the maternal TSH concentration was lower in the supplement group, the cord TSH concentration was 27% higher in the supplement group[50], suggesting that in iodine-deficient areas, the foetal thyroid gland may be particularly sensitive to the inhibitory effect of iodine.

Table 3 Changes in thyroid size measured by ultrasound during pregnancy in iodine-sufficient and -deficient countries.

Reference	Iodine status Country	*n*	Trimester (T) of pregnancy or time post-partum (PP)	Change in thyroid size
	Iodine sufficient			
78	Finland	7–21	1,2,3 T	No or small increase during pregnancy
79	Netherlands	10	Before pregnancy, 1,2,3 T	No increase during pregnancy
80	USA	16	3 T and 6 months PP	13% decrease after parturition
	Iodine deficient			
71	Belgium	33–172	1,2,3 T and 6 months PP	18% increase during pregnancy
10	Belgium	60	1,3 T	30% increase during pregnancy
81	Denmark	20	2,3 T and 3,6,12 months PP	20% increase during pregnancy
9	Denmark	24–26	2,3 T and 3,6 months PP	31% increase during pregnancy
82	Ireland	14–95	1,2,3 T and 6,12 months PP	15% increase during pregnancy
31	Italy	18	1,3 T	16% increase during pregnancy

Table 4 shows results from six randomised, controlled trials of iodine supplementation involving 450 pregnant European women with mild-to-moderate ID.

Romano *et al.*[31] gave 120–180 μg iodine as iodised salt daily or gave a placebo control beginning in the first trimester to healthy pregnant women ($n = 35$, median UI concentrations in the two groups 31 or 37 $\mu g\,l^{-1}$). In the group treated with iodine, the median UI concentration increased threefold and thyroid volume did not change[31]. In the controls, there was no change in the UI concentration, and had a 16% increase in thyroid volume[31]. Treatment had no effect on the maternal TSH concentration.

Pedersen *et al.*[9] randomised 54 pregnant women to receive either 200 μg iodine per day as a solution of potassium iodide or no supplement from 17 weeks of pregnancy to full term. The median UI concentration increased from 55 to 90–110 $\mu g\,l^{-1}$ in the treated group. The thyroid volume of women increased 16% in the treated group compared with 30% in the controls[9]. The concentration of Tg and TSH in women, and the concentration of cord Tg, were significantly lower in the treated group than in the controls[9]. No significant differences were found between groups in terms of the concentration of T_4, T_3 and fT_4 in maternal or cord blood[9].

Table 4 Randomised, controlled trials of iodine supplementation during pregnancy in mild-to-moderate iodine-deficient countries of Europe and the urinary iodine concentration before and after treatment.

Reference	Iodine dose ($\mu g\,day^{-1}$)	Urinary iodine concentration	
		Before treatment	After treatment
53	50	65[1]	128[1]
10	100	36[2]	80–90[2]
31	120–180	37[3]	100[3]
52	150	50[2]	105[2]
9	200	55[2]	90–110[2]
53	200	91[1]	230[1]
51	230	53[1]	104[1]

[1] $\mu g\,g^{-1}$ cr.; [2] $\mu g\,l^{-1}$; [3] $\mu g\,day^{-1}$.

In a double-blind, placebo-controlled trial, Glinoer *et al.*[10] supplemented 120 pregnant women who had a median UI concentration of 36 $\mu g\,l^{-1}$ and biochemical criteria of excess thyroid stimulation, with 100 μg iodine per day or gave a placebo control from around 14 weeks of pregnancy to full term. The treatment had no significant effect on the concentration of maternal or cord T_3, fT_4 and the T_3/T_4 ratio[10]. The treated women had a significantly higher UI concentration, a smaller thyroid volume and a lower concentration of TSH and Tg when compared with controls[10]. The newborn children of the treated group also had significantly higher UI concentration, a smaller thyroid volume and a lower Tg concentrations when compared with controls[10]. There was a 14% increase in the cord serum TSH concentration in the treated group, but it was not statistically significant.

Liesenkötter *et al.*[51] reported a quasi-randomised, controlled trial of 230 μg iodine per day given from the eleventh week of pregnancy to full term in 108 pregnant women with a median UI concentration of 53 $\mu g\,g^{-1}$ cr. and a goitre rate of 42.5%. The median UI concentration increased to 104 $\mu g\,g^{-1}$ cr. in the treated group, and the median thyroid volume was significantly lower in the newborns of the treated women compared with controls (0.7 vs. 1.5 ml, respectively)[51]. Treatment had no significant effect on the concentration of maternal TSH, T_3, T_4, Tg or on the thyroid volume, and had no effect on the concentration of TSH in the newborn[51].

In a placebo-controlled, double-blind trial, Nohr *et al.*[52] gave to 66 pregnant women who had antibodies to anti-thyroid peroxidase (TPO-Ab) a multi-nutrient supplement containing 150 μg iodine per day or a placebo control from the eleventh week of pregnancy to full term. The median UI concentration was significantly higher in the treated women at full term than in the controls, but there were no differences in the concentration of maternal TSH, fT_4 or Tg between groups[52]. There was no difference in the prevalence of anti-thyroglobulin antibodies (Tg-Ab) or TPO-Ab, and no differences between groups in the prevalence or severity of post-partum thyroid dysfunction (PPTD), defined as an abnormal TSH concentration in the

post-partum period. However, 12/20 (60%) treated women developed PPTD compared with 11/24 (46%) controls, and failure to detect a significant difference in the prevalence of PPTD may have been due to a type II error.

In a prospective, randomised, open-label trial, Antonangeli *et al.*[53] supplemented 67 pregnant women who had a median UI concentration of 74 $\mu g\,g^{-1}$ cr. with 50 or 200 μg iodine per day from 18–26 weeks of pregnancy to 29–33 weeks. The median UI concentration was significantly higher in group given 200 μg iodine per day than in the group given 50 μg iodine per day (230 vs. 128 $\mu g\,g^{-1}$ cr.).[53] However, there were no differences between groups in the concentration of maternal fT_4, fT_3, TSH and Tg or in thyroid volume, and no differences in the prevalence of TPO-Ab, Tg-Ab or PPTD.

In summary, in all of these trials, iodine supplements significantly increased the maternal UI concentration. The doses of iodine varied between 50 and 230 $\mu g\,day^{-1}$, and the data indicate no clear dose–response relationship for the concentration of UI, TSH, Tg, thyroid hormones or in terms of thyroid volume. Iodine supplements during pregnancy generally appear to be safe; there was no increase in the trials the prevalence of thyroid autoimmunity in mothers, or in the prevalence or severity of PPTD. However, the sample sizes were small and more data, particularly from TPO-Ab + women, would be valuable. In three of the five trials that measured the thyroid volume of mothers, supplementation was associated with a significantly reduced thyroid size. The studies also suggest that an increase in newborn thyroid volume and the concentration of Tg can be prevented or minimised by iodine supplementation. Although less consistent, the data also suggest that the concentration of maternal TSH is generally lower (within the normal reference range) with supplementation. Supplementation has little or no impact on the concentration of total or free thyroid hormones in mothers and newborn children. There are no clinical data on the effect of supplementation on birth weight or prematurity, and no data on long-term outcomes, such as maternal goitre, thyroid autoimmunity or child development.

Iodine intakes during lactation and urinary iodine and breast milk iodine concentrations

Since the mammary gland is able to concentrate iodine, the iodine supply to the newborn *via* the breast milk may be maintained even in the face of a maternal ID[54,55]. This may help explain why, in areas where there is an ID, BMIC is often greater than expected based on the UI concentration of lactating mothers[55,56]. The BMIC is strongly influenced by the mothers' iodine intake[58].

In the USA, Gushurst *et al.*[57] found that the median BMIC in women who consumed uniodised salt was 113 $\mu g\,l^{-1}$, while the median concentrations in women who consumed low or high amounts of iodised salt were 143 or 270 $\mu g\,l^{-1}$, respectively.

Several studies have compared the BMIC before and after supplementation with iodised oil or potassium iodide, or with untreated controls.

Pretell *et al.*[59] injected women with 950 mg iodine as iodised oil. The median BMIC at 18–36 months post-partum was 70 $\mu g\,l^{-1}$ compared with 2 $\mu g\,l^{-1}$ in mothers not receiving treatment.

In Algeria, Chaouki and Benmiloud[60] gave 240 mg iodine as oral iodised oil either 1–3 months before pregnancy or in the first or third trimester. At delivery and 6 month post-partum, the mean BMIC ranged from 520 to 559 $\mu g\,l^{-1}$ and from 307 to 346 $\mu g\,l^{-1}$, compared with 307 and 260 $\mu g\,l^{-1}$ in untreated women.

In 147 Danish mothers, the median BMIC on the fifth day post-partum was significantly higher (57 $\mu g\,l^{-1}$) in those receiving supplementation with 150 $\mu g\,day^{-1}$ of oral iodine, compared with women who were not supplemented (34 $\mu g\,l^{-1}$)[61].

In Germany, 60 mothers who received 200 $\mu g\,day^{-1}$ of oral iodine had a significantly higher mean iodine concentration in breast milk (76 $\mu g\,l^{-1}$) than untreated controls (55 $\mu g\,l^{-1}$)[62].

Although increasing the iodine intake of iodine-sufficient women can further increase BMIC[57], an iodine intake by an infant that is greater than requirements will simply be excreted in the urine. Thus, iodine requirements during lactation should be based on infant balance studies rather than on the measured but variable amount of iodine excreted in breast milk by women in iodine-sufficient countries. Based on the balance studies of Delange *et al.*[30], the full-term infant's requirement for iodine is about 90 $\mu g\,day^{-1}$, and this is the intake recommended by the WHO, UNICEF and the ICCIDD[15]. Based on a mean breast milk volume of 0.78 $l\,day^{-1}$ in the first 6 months of infancy[25], and assuming that 95% of the iodine in breast milk is absorbed, a BMIC of $\geq 120\,\mu g\,l^{-1}$ should cover the infant's iodine requirement of 90 $\mu g\,day^{-1}$ until weaning foods are begun. Most infants begin weaning by the second half of the first year of life, and some of the iodine requirement during that period will be met from weaning foods. Semba and Delange[58] proposed that a potential indicator of iodine status in a population could be the proportion of lactating women whose BMIC is $\geq 100\,\mu g\,l^{-1}$.

Table 5 shows the BMICs of women living in areas where people are iodine sufficient or have mild-to-severe ID. Among the iodine-sufficient countries, the BMICs of women in Switzerland and Sweden are less than the concentration required to meet an infant's needs (100–120 $\mu g\,l^{-1}$), while they are at, or above,

Table 5 The mean or median breast milk iodine concentration of women in iodine-sufficient and -deficient countries.

Reference	Country	$\mu g\,l^{-1}$
Iodine sufficient		
83	Finland	25–53
84	Japan	661
85	Japan	33–385
86	New Zealand	98–247
87	The Netherlands	10
88	Saudi Arabia	136–198
89	Saudi Arabia	149–204
90	South Korea	892
91	Sweden	93
92	Sweden	56
93	Switzerland	78
57	USA	60
94	USA	113–270
95	USA	142
Iodine deficient		
96	Australia	50
97	Belgium	54
91	Belgium	95
98	Ethiopia	5–16
99	France	74
100	France	70
101	France	82
102	Germany	7
103	Germany	55
91	Germany	25
104	Germany	93
105	Germany	18–25
106	Germany	30–34
92	Guatemala	60
92	Hungary	64
107	Italy	150
108	Italy	59
54	Italy	33–43
109	Morocco	27–40
110	Niger	40
92	Nigeria	62
92	Philippines	57
111	Reunion	18–54
112	Slovakia	81–89
113	Spain	100
114	Spain	109
115	Spain	77–100
116	Thailand	45–68
117	Turkey	109
56	Turkey	73
92	Zaire	15

this concentration in the Netherlands, the USA and Japan.

Although the requirement for iodine of a mother is large at 200–290 $\mu g\,day^{-1}$, after accounting for iodine losses in breast milk, the median UI concentration of lactating women that indicates adequate iodine nutrition should be similar to that of non-pregnant, non-lactating women, i.e. 100–199 μg per l[15]. Table 6 shows the UI concentrations reported from studies of lactating women in iodine-sufficient and -deficient countries. There are few data, the numbers of women in most studies are small, and breast-feeding status was often not clearly documented. The studies generally report a median UI concentration in lactating women that is similar to the general population, but almost all reports are from iodine-deficient countries, and show median UI concentrations $<100\,\mu g\,l^{-1}$.

Table 6 Urinary iodine concentration[1–3] in lactating women and in the general population or in non-lactating controls in countries of different iodine status.

Reference	Iodine status Country	*n*	Time post-partum	Urinary iodine	General population or controls
	Iodine excess				
37	Chile	19	3 months	459[1]	
	Iodine sufficient				
41	Singapore	230	6 weeks	105[2]	98[2]
			3 months	104[2]	
	Iodine deficient				
9	Denmark	26	1 week	30[2]	50[1]
		26	26 weeks	50[2]	
		26	52 weeks	58[2]	
39	Ireland	108	6 weeks	70[2]	70[2]
51	Germany	70	11 days	50[3]	
74	New Zealand	35	3,6,12 months	24–52[1]	24–47[1]
75	Nepal	1028	13 weeks	61[1]	
76	Sudan	47	3–9 months	30–63[2]	76[2]
56	Turkey	70	5 days	30[2]	

[1] $\mu g\,day^{-1}$; [2] $\mu g\,l^{-1}$; [3] $\mu g\,g^{-1}$ creatinine.

Iodine intakes during infancy

During infancy, the mean volume of breast milk consumed is about 0.78 l day^{-1} over the first 0–6 months[25] and some 60–65% of ingested water is excreted by the kidney[63]. Although there is a large day-to-day variation, the volume of urine daily in early infancy is estimated to be 30–55 ml kg^{-1} body weight[63–65] and the reference body weight for a child aged 0–6 months is 7 kg and for a child aged 6–12 months is 9 kg[25]. Based on these data, the volume of urine is estimated to be 0.4–0.5 l day^{-1} in early infancy. Therefore, considering the requirement for iodine of 90 μg per day[15], the median UI concentration indicating optimal iodine nutrition in infancy is estimated to be in the range of $\geq$180–220 μg per l[26].

Delange *et al.*[66] supplemented healthy infants and children aged 6 months to 3 years in Belgium who had a median UI concentration at baseline of 101 $\mu g\,l^{-1}$, with an dose of 90 $\mu g\,day^{-1}$ of iodine. After about 30 days of supplementation, the geometric mean UI concentration was beginning to plateau at 220–240 $\mu g\,l^{-1}$.

Table 7 shows the median UI in full-term newborns in countries with iodine sufficiency and varying degrees of ID. In general, among the iodine-sufficient countries, the median UI concentration varies from 96 to 167 $\mu g\,l^{-1}$, well below the estimated median UI concentration of $\geq$180–220 $\mu g\,l^{-1}$ that indicates an adequate iodine intake. More data are clearly needed, but the evidence available suggests that the iodine intake of many infants, even in countries designated as iodine sufficient, may be suboptimal.

Table 7 The median urinary iodine concentration of full-term infants in iodine-sufficient and -deficient countries ([1] = Mean).

Reference	Iodine status Country	*n*	$\mu g l^{-1}$
	Iodine sufficient		
119	Canada	81	148
119	The Netherlands	64	162
87	The Netherlands	36	150[1]
119	Sweden	39	112
105	Sweden	61	96
118	USA	50	921
	Iodine deficient		
118	Belgium	103	35
119	Belgium	196	48
120	Belgium	90	86
121	Czech Republic	50	79
119	France	82	58
119	France	37	29
105	Germany	461	12–29
119	Germany	87	28
122	Germany	177	31
122	Germany	213	44
123	Germany	22	50
124	Germany	32	95[1]
119	Germany	81	15
119	Germany	39	13
119	Germany	39	11
125	Hungary	209	35–75
126	Ireland	–	100[1]
119	Italy	114	47
119	Italy	14	71
127	Italy	195	56
128	Italy	9	67
56	Turkey	70	24

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