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Review

Iodine nutrition and breast feeding

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Abstract

A survey of the databanks Medline and Web of science identified studies dealing with maternal and infant iodine nutrition during breast feeding. The iodine concentration of human milk varies widely due to maternal iodine intake. Mean breast milk iodine concentrations are reported as ranging from 5.4 to 2170 µg/L (median 62 µg/L) in worldwide studies. In the few studies that compared length of lactation, gestation length, and parity number, these factors did not significantly affect milk-iodine concentrations. In studies of maternal iodine deficiency, untreated goiter had no impact on breast milk iodine when compared with controls. Iodine in human milk responds quickly to dietary iodine intake, either supplemented or consumed in natural foods. Easily absorbable iodine from foods, supplemental sources, iodine-based medication or iodine-based antiseptic solutions used during parturition, is taken up by the maternal thyroid and mammary glands through the Na^+/I^- symporter system. This transmembrane carrier protein transports iodine against a high concentration gradient. Hormonal iodine in breast milk occurs mainly as T-4, but depending on maternal iodine intake, high concentrations of the inorganic form (iodide) are found. In less developed countries, where natural-food-iodine intake is low, adequate maternal iodine nutritional status depends exclusively on enforcement of food iodination. In industrialized countries, maternal iodine intake has increased as a function of increasing consumption of dairy products. The human infant is sensitive to maternal iodine nutrition during fetal development and later during breast feeding. Environmental factors, not directly related to maternal iodine intake, such as intake of selenium and organochlorine pollutants, can affect thyroid hormone homeostasis in breast-fed infants. In spite of low iodine concentrations found in milk of mothers consuming low-iodine natural foods, long lasting or even life-lasting benefits to the breast-fed infant are demonstrable.

Key words: thyroid, symporter, goitrogens, lactation, goiter

Introduction

Iodine deficiency is the determining cause of endemic goiter. Although this is clinically the most recognizable effect, there are other iodine deficient disorders (IDD). In the pregnant and lactating woman, iodine deficiency is related to disorders that affect mothers and fetuses: increased early and late loss of gestation, intellectual disability, endemic cretinism, neonatal hypothyroidism, neonatal hyperthyroitropenemia, increased perinatal and infant mortality, and growth retardation (1). Due to its effect on brain development during gestation, iodine deficiency is considered the world's single greatest cause of easily preventable brain damage and mental retardation (2, 3).

In the past, iodine deficiency occurred more frequently in regions with iodine-depleted soil. Upon its recognition, public health policies to prevent iodine deficiency were successful and iodine prophylaxis, mainly through salt iodination, proved an inexpensive and effective measure. Certain areas of the world that adopted iodine supplementation reduced iodine deficiency, and increased breast milk iodine concentration. However, in areas where neglect in iodine-prophylaxis enforcement caused its dis-

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continuation, there has been a resulting increase in the incidence of goiter (4). Therefore, iodine deficiency remains a significant global health problem.

In industrialized countries however, improvement of living standards associated with increase in consumption of natural foods with high iodine content, have improved iodine prophylaxis (5), and eradicated goiter in some countries (6). According to Phillips (6) endemic goiter present in Britain until recently, progressively disappeared without direct interventive measures of food iodination. It is of interest, that changes related in farm practices, specially in the dairy industry, have increased iodine concentration in dairy products. In some areas excessive iodine consumption is raising public health concerns relative to thyrotoxicosis problems (7).

Total iodine in the human body depends on iodine nutritional status and reference values reflect such variation. Iodine in the human organism is concentrated in a specialized structure, the thyroid, where most of it is hormonal. Reference values for total body iodine were reported by some authors (8) as being between 30–50 mg with 30% of it being found in the thyroid gland, while others (9) have reported total body iodine to range between 15–20 mg and 70–80% stored in the thyroid. The iodine demand of newborns is partly supported by thyroid-iodine storage. Bakker et al. (10) observed significantly less urinary iodine in athyroitic infants. The human infant is born with a thyroid gland which is functional from the 11^{th} week of gestation (11) and is vulnerable to maternal iodine and thyroid status. At birth, an infant's thyroid gland, weighing approximately 18 g can store 180 µg I/mg DNA (12).

Thyroxine (3,5,3',5'-tetra-iodothyronine) is synthesized and stored in the thyroid gland. Its more active metabolite, 3,5,3'-triiodothyronine is formed after deiodination reactions. Two deiodinases, type I and type II 5'-deiodinase, catalyze the reductive 5'-(phenolic ring) of the prohormone L-thyroxine (3,3',5,5'-tetraiodo-L-thyroxine, T-4) to thyromimetically active 3,3'-5-triiodo-L-thyronine (T-3). Type III 5-deiodinase removes the iodide in 5-position from the tyrosyl ring of T-4 and forms thyromimetically inactive 3,3',5'-triiodothyronine (reverse T-3, rT-3). All three deiodinase isoenzymes are selenoenzymes (13) also present within tissues requiring local synthesis of T-3 (14). Animal studies showed that the mammary alveolar cell contains thyroxine-5'-deiodinases which are positively correlated to lactation intensity (15). Deiodinase activation is also present in milk cellular components (16).

Nonhormonal iodine is distributed in extra thyroidal tissues, but its function is not known (8). It is believed that iodine can counteract some impaired functions in organs of thyroidectomized rats (17). In iodine-deficient rats there are subtle differences in iodine and iodide utilization (18). Iodide *per se* in human serum showed an antioxidant effect *in vitro* (19). Another form of organic nonhormal iodine is that of iodolipids synthesized specifically for goiter prophylaxis from iodination of the unsaturated fatty acids of certain plant oils. These compounds are metabolized as a function of the iodinated fatty acid species. Contrary to iodized salt which is easily excreted, iodolipids can trap iodine in the body fat compartment. This iodine retention capacity depends on the species of the unsaturated fatty acid that binds iodine.

Iodine is easily absorbed from the gastrointestinal tract and avidly taken up by the thyroid gland, through the Na^+/I^- symporter (NIS), a transmembrane carrier protein. This specialized iodine uptake mechanism is also present in the lactating mammary gland (20) and allows the element to be absorbed against a high concentration gradient. The NIS in the mammary gland, which explains its long known capacity to take up iodine, is modulated by oxytocin and prolactin (21) and is inhibited by thiocyanate (22). Therefore, transient as well as long lasting conditions that may change maternal iodine blood levels modulate its secretion into breast milk. Nevertheless, the suggestion that iodine milk concentrations under "usual" conditions may range from 55 to 65 µg/L (23) is acceptable. Indeed, in spite of wide variation (Tables 2–4), the median iodine concentration from studies worldwide conducted after 1960 is within such range (62 µg/L). Earlier literature, reviewed up to the 1930s, is discussed elsewhere (24).

The objective of this review is to discuss iodine nutrition during breast-feeding, encompassing the complex interaction of iodine speciation in breast milk, and constitutional and environmental factors affecting maternal iodine metabolism during pregnancy and lactation.

Iodine species

Breast milk iodine concentrations (Tables 2–4) occur in a variety of chemical forms. The iodine covered in this review refers only to its stable form. Radioactive iodine isotopes used in medicine, or as a result of fallout have been extensively studied. The radioisotopes ^{131}I, ^{125}I, and ^{123}I, because of their relatively short half-lives (8 to 60 days) are largely used in nuclear medicine, and when administered to lactating mothers are easily secreted into breast milk. Numerous studies of its pharmacokinetics and a review of their secretion into breast milk, can be found elsewhere (25). Fallout ^{131}I (because of its relatively high fission yield of 2.9%), and the long lasting ^{129}I (half-life: $1.6 \cdot 10^7$ years), can accidentally be released from nuclear power plants. These radionuclides are also discussed by other authors (26).

The chemical species of iodine reported in human milk show substantial variations. Mean total iodine concentrations from reports around the world varied from 5.4 to 2170 µg/L resulting from consumption of natural-food iodine. Breast milk iodide, its inorganic form, is found in concentrations that reflect the maternal intake, its mean has been reported as varying from 44% (27) to 71–80% (28–30), with a range of variation within study of 21.3% to 98.5% (29). However, extreme high values of iodide in breast milk as a result of dietary iodine (31, 32) and skin and vaginal iodine-based antiseptic solutions absorbed by the mother (33–37) can greatly increase the relative amount of iodides. Organic iodine, mainly thyroid hormones (T-4, T-3, and metabolites), are also reported in breast milk with large variation in concentrations. Table 1 summarizes studies showing mean iodothyronine concen-

trations in breast milk, but its metabolic role in the infant is discussed elsewhere (38). Although thyroxine is the main thyroid hormone in human milk, large differences in iodothyronine concentrations among studies suggest that there are still unsolved questions regarding analytical methods. Less specific techniques such as competitive protein binding assay (CPBA), also radioimmunoassay (RIA) without previous extraction to eliminate interferences from lipids, tend to give higher concentrations. Bode et al. (39) reported T-4 evenly distributed between fatty (55%) and whey layers, while Moller et al. (40) found most of T-4 (>90%) in the whey fraction. There are few reports comparing assays for T-4 in breast milk (41, 42). Mizuta et al. (41) concluded that CPBA was unsuitable for measuring T-4 in milk, while Mallol et al. (42) reported that breast milk contains substances that interfere with RIA. Therefore, a representative value of iodothyronine concentrations awaits further studies.

As a consequence of low iodothyronine concentrations in breast milk, the proportion of total milk iodine contributed by these substances seems to be very small. Man and Benotti (43) attempted a quantification of thyroxine-like iodine substances in breast milk. They found 4.7% of butanol extracted iodine in 5-day colostrum. However, Mallol et al. (44) reported that in milk samples with a mean iodine of 77 µg/L, T-4 and T-3 were respectively 0.42 and 0.09 percent of iodine. Within the organic iodine fraction of human milk, Etling and Gehin-Fouquet (28) measured iodinated (T-4, T-3, monoiodotyrosine) compounds and found the monoiodotyrosine representing 40% of organic iodine, while T-4 and T-3 were respectively 2.5 and 1.5%.

Any of the thyroid hormones or their metabolites that reach the maternal blood stream can appear in breast milk. Mammocyte deiodinases that convert T-4 into T-3 may play a role in the breast milk iodothyronine concentrations. Animal studies suggest that in the mammary gland deiodinase increases during early lactation as a function of increase in milk yield (15). Assuming that the 5'deiodinase expression in the rat's mammary gland induced by lactation (15, 21) is also present in the lactating woman, iodothyronines in breast milk then occur as a function of maternal serum T-4 and rate of 5'deiodination. Studies summarized in Table 1 suggest that concentrations of T-3 may increase from colostrum to more mature milk, although in some studies it was not statistically significant (45–46). Whereas for thyroxine, Bode et al. (38) showed that milk produced during pregnancy had twice as much T-4 (14 *vs* 7 µg/L) than postpartum breast milk. Most studies showed an increase in breast milk T-4 (46–50), except Tenore's (51).

Slebodzinski et al. (52) reviewed the role of thyroxine deiodinases on iodothyronine concentrations in milk of several species. While T-4 represents a small fraction of that found in serum, milk T-3 is approximately 1/3 of serum T-3. They concluded that T-3 in milk is poorly related to its diffusion from serum, and that there is no relationship between T-3 in serum and milk, except in early lactation. Animal studies showed that the presence of T-3 in milk is originated from serum transference, and from T-4 deiodination within the mammary gland (16). Inflammation of mammary tissues (mastitis) significantly reduced milk T-3 content. During altered thyroid conditions, like hyperthyroidism (Graves and Hashimoto diseases) and goiter (41) in lactating mothers, T-4 was not detected but T-3 was secreted in breast milk at concentrations comparable to euthyroid subjects (Table 1). Work is still needed to establish the contribution of exogenous thyroid hormones and their role in the breast-fed infant.

The advent of iodine prophylaxis through iodized oil has revealed the potential of adipose tissue to affect iodolipid metabolism. Furnee et al. (53) showed a faster urine iodine elimination rate from iodized fatty acid in ethyl-esters than from iodized fatty acids in triacylglycerol. The iodine radiotracer studies of Ingenbleek et al. (54) showed differences in iodine secretion due to the iodinated fatty acid. Adults excreted 66% of ^{127}I from oral intakes of Lipiodol (iodized poppyseed oil) and 49% of Brassiodol (iodized rapeseed oil). They proposed that sequestration of ^{127}I was a feature of the unique presence of eructate in Brassiodol (54). They also discussed metabolic differences pointing that the mobilization of fatty acid increases with unsaturation for a given chain length, and decreases with increasing chain length for a given unsaturation. Higher iodine retention was reported for iodized peanut oil compared to poppyseed oil (55).

Differences in the species of unsaturated fatty acids modulate iodolipid metabolism that in turn affects iodine release from the body fat pools. Adipose tissue *per se* also seems to influence storage of iodolipids. Fierro-Benitez et al. (56) showed that the half-life retention of iodine from Ethiodol was approximately half in malnourished children compared to controls. The metabolic characteristics of iodolipids make these compounds more effective than KI for goiter prophylaxis in remote areas (57), with the advantage of a better safety record (58). Complexation of iodolipids and its release from the lipid compartment, coupled with differences in the rate of iodolipid dehalogenation, attenuate thyroid exposure to iodide excess. The physiological and pharmacological effects of high iodine supplements as iodolipids were reviewed by Wolff (58). Indeed thyroidal complications resulting from excess iodine are much rarer after iodine supplementation with iodolipids than with KI (58). Such studies however have not yet been carried out in lactating women or breast-fed infants.

The fetal fat metabolism seems to change rapidly in the postnatal period. The human fetus starts accumulating fat after 26 weeks, reaching 1/3 of total body weight at the time of birth. Between the 40^{th} and 42^{nd} week of gestation however, there is a distinct fall in fetal fat deposition. Also the proportion of fetal lipids in the adipose tissue compartment is only 45% between the last trimester of pregnancy until 4 months of age. This proportion increases to adult levels (90%) by one year of age (59). This peculiarity in fat metabolism during transition from intra- to extra-uterine life should be considered in maternal iodine-supplement studies.

Certain types of iodine-containing drugs such as benzofuranic derivatives (amiodarone), that are also lipophilic substances, taken during pregnancy, are also found in breast milk even after 5 weeks of discontinuation (60).

Table 1. Summary of studies comparing thyroid hormone concentrations in breast milk.

Reference	T-3 µg/L	T-4 µg/L	Metabolite ng/L	Stage of lactation, analytical method
Bode et al. (39)	1.36	14	58[1]	Third semester pregnancy
	2.86	7	62[1]	1–4 m, RIA
Etling & Gehin-Fouque (28)	0.34	0.57	(6–20)[2,3]	NG
Ibrahim et al. (134)	0.214	22.9	–	3–21 d, RIA
Jansson et al. (45)	0.53	<2.38	–	Colostrum, fore-milk, RIA
	0.62	<2.38	–	Colostrum, hind-milk
	0.79	<2.38	–	Mature
Karimova et al. (49)	0.33	39	–	1 d, RIA
	0.61	51	–	3 d
	1.99	106	–	6 d
Mallol et al. (42)	–	0.71	–	NG, RIA after extraction
Mallol et al. (44)	ND	0.46	–	1 w, RIA after extraction
	ND	0.73	–	2 w, RIA after extraction
	ND	0.31	–	>5 w, RIA after extraction
	0.12	0.52	–	Total mean
Man and Benotti (43)	–	3.3	–	5 d, butanol extracted I
Mizuta et al. (41)	(0.26–1.12)	ND	–	*7d–7m, Graves, RIA
	(0.59–1.11)	ND	–	**7d–7m, Hashimoto, RIA
	0.82	ND	–	***7d–7m, RIA
Moller et al. (40)	–	4	–	Selected ion monitoring
Montalvo et al. (50)	0.38	6	–	1 d
	1.13	96	–	1 w
	0.99	21	–	1 m
Nabukhotnyi et al. (46)	0.33	79.5	–	Colostrum
	6.13	214.8	–	Transition
	7.4	321		Mature
Nizankowska-Blaz et al. (135)	0.75	ND	–	5 d,RIA
Oberkotter (136)	6.69	–	–	Monoiodothyronine
Oberkotter and Tenore (137)	2.75	1.21	–	RIA, T-3 = primary peak
	0.86	–	–	Secondary peak
Sack et al. (138)	–	3.8	–	3–77 d, RIA
	–	42.7	–	8–48 d RIA
	–	11.1	–	59–165 d, RIA
Sack et al. (139)	–	7	–	1–5 d, RIA
	3.86	31	–	6–49 d
	–	14	–	>50 d
Salakhova et al. (48)	0.34	39	–	1 d, RIA
	0.61	51	–	3 d,
	1.99	106	–	6 d,
Sato and Suzuki (140)	<5	ND	ND	1–33 w
Slebodzinski et al. (141)	0.2	1.6	–	<24 d, RIA
Strbak et al. (47)	–	13	–	3 d, competitive binding assay
	–	76	–	3 m
	–	54	–	1 m
Tenore et al. (51)	–	40	–	1–2 m
	–	16	–	2–4 m
	–	13	–	4–6 m
Varma et al. (142)	0.350	ND	0.11[1]	1 d
	0.390	ND	0.124[1]	2 d
	1.32	ND	0.142[1]	3–7 d
	2.78	ND	0.148[1]	8 d

[1]reverse T-3; [2]Monoiodotyrosine; (range) [3]µg/L; RIA = Radioimmunoassay; ND: not determined; NG: not given;
*Graves' disease; **Hashimoto's disease; ***Goitrous mothers

Animal studies showed that amiodarone and its main metabolite desethylamiodarone, are easily transferable to rat pups through milk and distributed into neonatal tissues (61). The human mammary gland has also the ability to concentrate the iodinated drug and its desethyl metabolite. The maternal milk to plasma ratio varied from 2.4 to 13 for amiodarone and 1 to 2.9 for desethylamiodarone (60, 62–63). These iodinated lipophilic substances are metabolized as a function of body lipid pools with half-lives comparable to iodolipids. Amiodarone half-life has been estimated to 100 days (64) while iodolipid half-lives range from 2.2 to 7.5 months (58).

Maternal constitutional factors

Relatively few studies have addressed maternal constitutional factors that could affect breast milk total iodine (Table 2). Studies that explored changes in total iodine milk concentrations due to length of lactation reported no significant correlation between milk iodide and the infant's age (65), and no significant differences (66–69) due to stage of lactation, but others found a significant decrease in 60 (70) and 90 day (71) milk iodine. The study of Seibold-Weiger et al. (69) provided data ranging from 1 to 12 weeks with and without iodine supplementation. Although there was a significant increase due to iodine intake, no significant differences were observed for the length of lactation studied. So far, no significant differences were observed due to the sampling time of the day (70), within individuals (65), between fore- and hind-milk (72), or between right and left breast (71). However there are claims that cracked nipples or breast engorgement cause a decrease in milk iodine concentration (71). Also, there was no significant difference between iodine milk of term and preterm mothers (29, 67) or due to maternal age (71).

It is important to notice that studies claiming significant differences (70–71) did not use appropriate statistical methods, as well as not indicating the procedures used. It is likely that the small number of degrees of freedom in Younes et al. (71) could not discriminate true variable effects from artifacts. Also comparing sets of variables *per se* does not measure additional variability of interactive factors, or inherent bias.

In spite of noticeable thyroidal stress during the first 3 months postpartum partly due to additional iodine loss in breast milk (73), the glandular stress seems higher in pregnancy (74). A study by Tajtakova et al. (75) however, showed that a higher mean thyroid volume was accompanied by a lower total milk iodine in multiparous mothers, but there was no significant difference from primiparous mothers. However, it seems that a compensatory mechanism enhances iodine uptake by the mammary gland of iodine deficient mothers (76). Indeed in maternal iodine deficiency studies there was no significant difference in milk iodine between treated and untreated goitrous moth-

Table 2. Summary of studies comparing iodine concentrations (µg/g or µg/mL) in breast milk related to maternal constitutional conditions.

Reference	Country	Group-1 (control)	Group-2	Stage of lactation, group-2
Ares et al. (67)	Spain		100	6–40 d, Term and Preterm
Beckers et al. (143)	Belgium		54	NG, Term and Preterm
Bruhn et al. (72)	USA		142	2–4 m, Fore- and hind-milk
Etling et al. (29)	Italy	43.5[1]	46	2–32 d, Preterm 26–32 w
			49.2	2–32 d, Preterm 33–36 w
			37–42 w	
			41.1	Colostrum
			50.4	Transition
			59	Mature
Heidemann et al. (77)	Germany	25	17.5	5 d, Goitrous
Johnson et al. (70)	N. Zealand		144.6	30 d
			124.3	< 60 d
			49.5	> 60d
Peiker et al. (66)	Germany	21.5[2]	25.5	5–6 d, Goitrous untreated
			17.6	5–6 d, Goitrous treated
		20.7[2]	32.2	4 w, Goitrous untreated
			17.7	4 w, Goitrous treated
Tajtakova et al. (75)	Slovakia		89	4–7 d, Total
		105[3]	81	Primipara, multipara
Trabzuni et al. (68)	Saudi Arabia		140.6	Maternal age 17–25 y
			136.2	Maternal age 26–35 y
			197.6	Maternal age >35 y
Younes et al. (71)	Saudi Arabia		191.2	0–30 d
			204.6	30–60 d
			169.9	60–90 d
			149.2	> 90 d

[1]Gestational age 37–42 w; [2]Euthyroid; [3]Primipara; NG: not given

ers (66). Furthermore, breast milk iodine in goitrous mothers may (77) or may not (66) show a significant decrease compared with controls.

Maternal medication and goitrogen consumption

During pregnancy and lactation, maternal thyroid disorders requiring treatment with antithyroidal drugs does not seem to affect the infant's thyroid function during breast-feeding. There are studies showing that propilthyrouracil (PTU), metimazole, and carbimazole (78–80) administered to breast-feeding mothers for the treatment of hyperthyoidism does not affect the thyroid function in breast-fed infants. One of these drugs, PTU, was found in low concentrations in breast milk. Only 0.025% of an administered dose of PTU was found 4 hours later. The maternal blood-serum to milk ratio was 7.7:0.7 (79). Inhibition of deiodination activity by PTU is low (ca. 10%) in human milk (52).

Anti-thyroid substances present in natural foods and recreational drugs have also been studied. Although cigarette smoking can be related to thyroid disorders (81), so far few studies with smoking mothers addressed breast milk iodine or thyroid status of breast-fed infants. Thiocyanate, due to cigarette smoking during pregnancy, correlated inversely with infant's birth weight. Its concentration in breast milk however, was considerably lower than in maternal serum (82). In areas of endemic hypothyroidism caused by natural-food thiocyanate, such goitrogens were found at low concentrations in breast milk. The mean thiocyanate ratio between maternal serum and milk was 133:57 (83). As a consequence of its low breast milk concentration, hypothyroidism was more frequent in 5–7 year olds than during breast-fed-aged child. The low passage of thiocyanate from maternal serum to breast milk seemed to protect breast-fed infants. In such cases signs of hypothyroidism appeared much later after weaning when children were on an adult style diet (83). In a subsequent study, it was shown that infant's serum thiocyanate levels dropped during breast-feeding and increased after weaning (84).

Maternal psychological conditions treated with lithium-based medications can affect thyroid status. Lithium competes with iodine for thyroidal uptake. Its concentration in the thyroid inhibits iodotyrosine coupling, alters the thyroglobulin structure, and inhibits the thyroid hormone secretion, which *per se* increases thyrotropin (TSH). Although there have been reports of hypothyroidism associated with the use of lithium-based medication (85) few studies dealt with milk lithium composition or breast-feeding.

In cases of maternal treatment with lithium studied by Schou and Amdisen (86), milk lithium concentrations ranged from 836 to 4164 µg/L. Naturally occurring breast milk lithium is low but varies widely among reports. Durrand and Ward (87) reported ranges from <19 to 23 ng/L in the UK, while Rossipal and Krachler (88) reported ranges from <80 to 1300 ng/L for Austrian mothers. The highest mean (390 µg/L) was reported by Hurgoiu and Caseanu (89) in Rumanian mothers and the lowest (6.5 ng/L) was reported in American mothers (90). Little is known about the lithium passage from blood-serum to breast milk, but based on a Schou and Amdisen (86) study it is lower than the iodine uptake in the mammary gland. Contrary to the iodine uptake that can reach 20 to 30 times maternal serum concentration, Schou and Amdisen (86) showed a mean of 2.6:1 ratio of maternal serum to breast milk. Rossipal et al. (91) found a strong concentration gradient mode of action for breast milk lithium transfer. Concentrations of lithium were comparable in all pairs of maternal sera and colostrum. Schou and Amdisen (86) found the breast milk lithium concentration was about half that in maternal serum but similar to the infant's serum. Nevertheless, the breast milk lithium concentration was toxic in one case of 4.16 mg/L reported by Tunnessen and Hertz (92).

Topical and internal iodine-containing medication used during pregnancy and lactation are transferred to breast milk. Iodine-containing antiseptic solutions (like povidone-iodine) used around parturition are easily absorbed by the maternal skin and passed into breast milk (33–37) with adverse effects to the breast-fed infant (37, 93). When used during pregnancy it can cause fetal and neonatal hypothryroidism and goiter (94). Iodide from antiseptic solutions is easily eliminated and breast milk iodine can fall back to normal concentrations within a week (95). Casteels et al. (37) reported that a mean milk iodine concentration could fall from 4410 µg/L to background concentrations (29–409 µg/L) within 8 days after discontinuation. Amiodarone, an iodine-rich (39.3% iodine) benzofuranic derivative used to treat tachyarrhythmias, because of its highly lipophilic characteristic is extensively distributed in tissues and can be secreted into breast milk long after its administration. After taking the drug (400 mg/day) throughout pregnancy and lactation, 14 day-milk samples showed concentrations of 2.6 to 13.3 mg/L for amiodarone and 0.73 to 5.7 mg/L for desethylamiodarone (62–63). The calculated total iodine concentration from the drug and its desethyl metabolite ranged from 1535 to 7587 µg/L (Table 3).

Environmental factors

Studies of environmental factors affecting milk iodine concentrations are shown in Tables 3 and 4. Table 4 illustrates total iodine milk concentrations comparing regions with endemic goiter. The comparison of breast milk iodine between goiter endemic and non-endemic regions within the same studies showed higher values of iodine concentrations in non-endemic goiter regions of Italy (76), Morocco (96) and between Sweden and Germany (97). Also in Thailand there were significant differences in breast milk iodine concentrations within areas of endemic goiter (98). Recently Cherinet and Kelbessa (99) reported that in areas of high prevalence (24 to 91%) of goiter in children, breast milk iodine was also low.

The multicenter study of Parr et al. (100), showed breast milk iodine concentrations varying from 15 to 69 µg/g. Among the countries studied (Guatemala, Hungary,

Table 3. Summary of studies comparing breast milk iodine concentrations (µg/g or µg/mL) due to iodine supplementation or contaminants.

Reference	Country	Groups		Description of test group
		Control	Test	
Arena Ansotegui et al. (34)	Spain	105	1216	Povidone-I
Bulux et al. (109)	Guatemala	101	90	Parasite treated
		98321	97329	Parasite treated
		2382	28579	Parasite treated
		615	788	Parasite treated
		381	375	Parasite treated
Casteels et al. (37)	Germany	(29–490)	4410	Antiseptic iodide
Chaouk and Benmiloud (108)	Algeria	307	520	I-sup 1–3 m before conception
		559		I-sup 1 m pregnancy
		551		I-sup 3 m pregnancy
		260	307	I-sup 1–3 m before conception
			346	I-sup 1 m pregnancy
			386	I-sup 3 m pregnancy
Eber et al. (35)	Austria	(40–180)	(320–2620)	Iodophors
Kevany et al. (105)*	Peru	(0–5)	97	2 mL iodized oil
		19		0.2 mL iodized oil (475 mg I/mL)
Koga et al. (36)	Japan		939.0	Povidone-I during and after delivery
			761.4	Povidone-I during delivery
			621.8	Povidone-I after delivery
			647.2	Benzethonium chloride
McKenna et al. (62)	UK	ND	7587	I as amiodarone and desethylamiodarone
Meng and Schindler (103)	Germany	(14–36)	(86–95)	1982–1992, 1994–1996 after I supplement
Moon and Kim (32)	Korea	892	2170	Seaweed
Muramatsu et al. (31)	Japan		(80–7000)	Algae consumption
Nohr et al. (104)	Denmark	33.6	57	All regions-supplemented
		54	62.5	Arhus-supplemented
		21.5	16.5	Randers-supplemented
		36	41.5	Aalborg-supplemented
		54.5	91.5	Copenhagen-supplemented
		28.7	57	Ringkorug-supplemented
Plomp et al. (60)	Netherlands	ND	(12–1944)	I as amiodarone and desethylamiodarone
Pretell et al. (106)*	Peru	(0–5)	97	2 mL iodized oil
			19	0.2 mL iodized oil (475 mg I/mL)
Seibold-Weiger et al. (69)	Germany	55	76	Supl 200 µg/d
		64	117	Supl 200 µg/d
		56	58	Supl 200 µg/d
		70	56	Supl 200 µg/d
		101	66	Supl 200 µg/d
		102	39	Supl 200 µg/d
		49	39	Supl 200 µg/d
		101	28	Supl 200 µg/d
Strunge et al. (63)	Denmark	ND		I as amiodarone and desethylamiodarone
Tiran et al. (102)	Austria	28	50	1990, 1992 after supplement
Trabzuni et al. (68)	Saudi Arabia	138.3	169.7	iodized salt

( ) range; *apparently same data; ND: not determined

Table 4. Summary of breast milk iodine concentrations (μg/g or μg/mL) in studies.

Reference	Country	I	Comments
Aquaron (144)	France	74	
Aquaron et al. (107)	Niger	40	Goitrous area
Aquaron et al. (96)	Morocco	27	Tengourt, endemic goiter
		40	Casablanca, non endemic
Bakker et al. (10)	The Netherlands	103	
Bauch et al. (145)	Germany	7.3	Karl-Marx-Stadt/1985
Bohles et al. (115)	Germany	55	
Cherinet and Kelbessa (99)	Ethiopia	12.7	Kodwono
		14.4	Sankura
		5,4	Tebmenjayaz
		15,7	Billalo
Chiba and Ichikawa (146)	Japan	33–385	
Chierichi et al. (147)	Italy	150	
Delange et al. (148)	Germany	25	Friburg
	Sweden	93	Stockholm
	Belgium	95	Brussels
	Sweden	93	Stockholm
Etling and Gehin-Fouque (28)	France	81.6	
Etling et al. (149)	Italy	54	Verona
Fernandez-Sanchez et al. (27)	Spain	108.5	
Gokmen and Dagli (150)	Turkey	109	
Gushurst et al. (65)	USA	113	Level of salt intake
		143	Level of salt intake
		270	Level of salt intake
		136	Level of cow's milk intake
		175	Level of cow's milk intake
		261	Level of cow's milk intake
Heidemann et al. (77)	Germany	93	
Heidemann et al. (97)	Germany	17.5	Goitrous area
		25	Control
Heinrich et al. (151)	Germany	13	Jena
Hoang-Truang et al. (152)	Switzerland	78	
Jaffiol et al. (153)	Reunion Islands	18–54	
Jansson et al. (45)	Australia	49.5	
Kosta et al. (154)	Yugoslavia	319	Dry weight, colostrum
		274	Dry weight, transitional
		660	Dry weight, mature
Lahesmaa and Vilkki (155)	Finland	53.3	Non-goitrous area
		25.1	Goitrous area
Mallol et al. (44)	Spain	77	Madrid
		100	Madrid
Man and Benotti (43)	USA	60	
Parr et al. (100)	Guatemala	60	
	Hungary	64	
	Nigeria	62	
	Philippines	57	
	Sweden	56	
	Zaire	15	
Pongpaewe et al. (98)	Thailand	45	Chumpae
		68	Sricchompu
		49	Prepaman
		51	Total
Schulze and Stotzfus (156)	USA	167.5	Pooled
Texier (157)	France	70	
Vermiglio et al. (76)	Italy	32.5	Endemic region
		43.3	Control
Wayne et al. (158)	NG	28	
Wiechen and Koch (159)	Germany	30–40	
Working Party (160)	UK	70	
Yamamoto et al. (161)	Japan	661	

NG: not given

Nigeria, the Philippines, Sweden, and Zaire) some of them (Hungary, Guatemala, Zaire) are goiter endemic zones. Hungary and Guatemala showed similar values that are 2 fold higher than Zaire (15 µg/L). Such variation stresses environmental factors other than iodine depleted soil where crops are grown.

Phillips (6) summarized data from Britain showing that changes in farming practices brought about the use of iodophores in sanitizing equipment as well as iodine supplementation of animal feed and raised the iodine concentrations in cow's milk. The encouragement of milk consumption greatly increased the iodine intake of the population in the USA (65) and the UK (6). However the most striking results of breast milk iodine increase due to iodine in natural food were seen in Korean (32) and Japanese lactating mothers (31) consuming algae and seaweed containing high concentrations of iodine. The early milk of these women had an iodine concentration 10 fold higher than the highest mean value reported in the literature (Tables 2–4). Edmonds and Morita (101) reviewed the nature of organic iodine compounds in marine plants.

Table 3 summarizes studies of milk iodine as a result of supplements or related to natural food iodine consumption. Salt iodination seems to be an effective measure to raise iodine concentrations in breast milk. Tiran et al. (102) showed that two years of supplementation of 10–20 µg KI/kg with salt doubled the median iodine concentration (28 to 50 µg/L) in breast milk in Austria. In Germany, breast milk iodine increased from 14 µg/L in 1982 to 95 µg/L in 1996 as a result of maternal iodine prophylaxis (103), while in Denmark, Nohr et al. (104) showed differences in breast milk iodine due to iodized salt supplementation in several regions. In the USA, Gushurst et al. (65) demonstrated that consumption of either iodized salt or commercially available milk caused equivalent increases in breast milk iodide concentrations. Mean iodine concentration from early studies (1936–1969) reviewed by Gushurst et al. (65) were much lower than the iodide values they reported. In Saudi Arabia however, Riyadh mothers consuming iodized salt showed a significant increase in urine iodine but the increase in milk iodine was not significant (68). Perhaps confounding dietary factors such as milk consumption reported by the study as the main source of food iodine could increase variability.

A more pronounced impact of maternal iodine prophylaxis on breast milk iodine was shown in studies using iodolipid supplements (Table 3). In spite of differences in oleic and linoleic acids between iodized poppyseed and peanut oil, both were effective in raising total iodine in breast milk (105–109). The work of Bulux et al. (109) showed a sharp increase in milk iodine that was not affected by maternal intestinal parasites. The iodine species derived from maternal iodolipids reaching breast milk is probably iodide, although so far there are no studies attempting iodine speciation in milk of iodolipid supplemented mothers.

The thyroid function during early life in the breast-fed infant can be affected by environmental factors not directly related to iodine supply of breast milk. There are animal studies showing interactions between selenium and iodine, and also altered thyroid hormone homeostasis due to polychlorinated biphenyls. Zimmerman et al. (110) found that Se deficiency diminishes the thyroid response to iodine supplementation. The severity of Se deficiency was inversely correlated with a change in thyroid volume and TSH. So far there are no studies related to breast milk. Organochlorine contaminants present in breast milk were significantly correlated with T-3 and T-4 (111), and with TSH (112–113) in the blood of breast-fed infants. These contaminants are persistent in the adipose tissue of mothers and may affect the infant in the uterus (112–113). Deiodination reactions that regulate the synthesis and storage of thyroid hormones are catalysed by selenoenzymes (13), that along with other thyroid hormone metabolizing enzymes can be affected by environmental organohalogens (114).

Breast feeding and infant's iodine status

The human infant is sensitive to maternal iodine nutrition mainly during fetal development. Besides showing a high and positive correlation between iodine in urine and breast milk (104), the thyroid volume in neonates is also associated with the maternal iodine status and breast milk iodine concentration (115). Beaufrere et al. (116) summarized studies from Europe showing that the countries with the lowest breast milk iodine concentrations also had low iodine values in breast-fed infant's urine.

Bohles et al. (115) observed that in spontaneous thyroid volume development during the first 3 months of life, exclusively breast-fed infants showed the greatest reduction in comparison to formula-fed (with and without iodine supplementation), or partially breast-fed infants. Bakker et al. (10) found that in the early days after post partum there is a temporarily negative iodine balance in healthy term babies. Indeed, urinary iodine excretion in 3 day-old neonates were greater in breast-fed than in bottle-fed infants (117). However, in older breast-fed infants the urinary iodine is more sensitive to dietary intake. Urinary iodine at three months was lower in breast-fed than in iodine-supplemented-formula-fed infants (118), but no significant differences were found between controls and malnourished (low mid-upper-arm circumference) breast-fed infants (119). Infant's serum T-4 and T-3 were significantly higher in breast-fed compared to formula-fed term (120) and preterms (121). Also breast-fed infants of mothers with thyroid malfunctions (goiter, Graves and Hashimoto diseases) showed serum thyroid hormones comparable to formula-fed infants (21). Furthermore, long lasting effects of breast-feeding on the thyroid function was observed after 3 years (122).

The advantages of breast-feeding is indisputable. However in iodine nutrition, there is speculation that a "biochemical imprinting" may operate in breast-fed infants (123). The role of breast-feeding on the thyroid function in later life was investigated by Phillips et al. (123) on women aged 60–71 years. In women that were breast-fed beyond one year, free T-4 were increased, whereas in women that were bottle-fed, serum TSH rose and free T-4 fell with increasing birth weight. The authors hypothe-

sized that a "set point of thyroid function in the adult is determined by fetal growth and infant feeding". In euthyroid infants, studies may (124) or may not (125) show significant effects on the thyroid function between breast- and bottle-fed infants. However, in most cases of neonatal hypothyroidism, breast-feeding was beneficial (10, 38, 126).

Even in circumstances of low total iodine concentration in breast milk, its metabolic effect is superior than in cow's milk based formulas (127). The newborn demands for iodine not stored in the thyroid during fetal development is sufficiently provided by breast milk even in cases of athyroidism (38) or congenital hypothyroidism (10). Iodine and thyroid hormones in breast milk are well absorbed and prevent impaired neurological development in the athyroic infant (38). In one study however, no differences in infant's plasma TSH, T-4, T-3, bone maturation, and psychological performance was found (128). In spite of higher urinary iodine in formula-fed infants (118–119), serum concentrations of thyroid hormones were reported as being higher in breast-fed infants (124).

Excess iodine causes thyrotoxicosis due to thyroid hormone inhibition (124). Extremely high milk iodine concentrations may pose risks of thyrotoxicosis to the breast-fed infant of mothers exposed to excess iodide in medications. Mothers consuming iodine-rich foods can concentrate even larger quantities of iodine in milk than in cases of iodine contamination from iodophors in antiseptic solutions (Tables 2–4). Consumption of iodine-rich seaweed is known to be associated with thyroid dysfunction (129) and has been recently linked with increased prevalence of sub-clinical hypothyroidism (130). However, there are no reports of adverse effects to the breast-fed infants. In such cases, natural food like algae, which is also rich in selenium, could be a possible intervening factor. In cases of maternal iodine supplements with iodolipids, there are also no reports of adverse effects to the breast-fed infant. In fact, in underdeveloped countries with a high prevalence of IDD, maternal supplementation with iodized oil protected breast-fed infants from hypothyroidism for three years (131) and could also decrease the mortality rate in this type of children (132).

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